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(57) Abstract

The sequences of nucleic acids encoding proteins required for E. coli proliferation are disclosed. The nucleic acids can be used to express proteins or portions thereof, to obtain antibodies capable of specifically binding to the expressed proteins, and to use those expressed proteins as a screen to isolate candidate molecules for rational drug discovery programs. The nucleic acids can also be used to screen for homologous genes that are required for proliferation in microorganisms other than E. coli. The nucleic acids can also be used to design expression vectors and secretion vectors. The nucleic acids of the present invention can also be used in various assay systems to screen for proliferation required genes in other organisms as well as to screen for antimicrobial agents.

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Description

GENES IDENTIFIED AS REQUIRED FOR PROLIFERATION IN ESCHERICHIA COLI

BACKGROUND OF THE INVENTION

Since the discovery of penicillin, the use of antibiotics to treat the ravages of bacterial infections has saved millions of lives. With the advent of these "miracle drugs," for a time it was popularly believed that humanity might, once and for all, be saved from the scourge of bacterial infections. In fact, during the 1980s and early 1990s, many large pharmaceutical companies cut back or eliminated antibiotics research and development. They believed that infectious disease caused by bacteria finally had been conquered and that markets for new drugs were limited. Unfortunately, this belief was overly optimistic.

The tide is beginning to turn in favor of the bacteria as reports of drug resistant bacteria become more frequent. The United States Centers for Disease Control announced that one of the most powerful known antibiotics, vancomycin, was unable to treat an infection of the common Staphylococcus aureus (staph). This organism is commonly found in our environment and is responsible for many nosocomial infections. The import of this announcement becomes clear when one considers that vancomycin was used for years to treat infections caused by stubborn strains of bacteria, like staph. In short, the bacteria are becoming resistant to our most powerful antibiotics. If this trend continues, it is conceivable that we will return to a time when what are presently considered minor bacterial infections are fatal diseases.

There are a number of causes for the predicament in which practitioners of medical arts find themselves. Overprescription and improper prescription habits by some physicians have caused an indiscriminate increase in the availability of antibiotics to the public. The patient is also partly responsible, for even in instances where an antibiotic is the appropriate treatment, patients will often improperly use the drug, the result being yet another population of bacteria that is resistant, in whole or in part, to traditional antibiotics.

The bacterial scourges that have haunted humanity remain, in spite of the development of modern scientific practices to deal with the diseases that they cause. Drug resistant bacteria are now advancing on the health of humanity. A new generation of antibiotics to once again deal with the pending health threat that bacteria present is required.

Discovery of New Antibiotics

As more and more bacterial strains become resistant to the panel of available antibiotics, new compounds are required. In the past, practitioners of pharmacology would have to rely upon traditional methods of drug discovery to generate novel, safe and efficacious compounds for the treatment of disease. Traditional drug discovery methods involve blindly testing potential drug candidate-molecules, often selected at random, in the hope that one might prove to be an effective treatment for some disease. The process is painstaking and laborious, with no guarantee of success. Today, the average cost to discover and develop a new drug is nearly US \$500 million, and the average time is 15 years from laboratory to patient. Improving this process, even incrementally, would represent a huge advance in the generation of novel antimicrobial agents.

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Newly emerging practices in drug discovery utilize a number of biochemical techniques to provide for directed approaches to creating new drugs, rather than discovering them at random. For example, gene sequences and proteins encoded thereby that are required for the proliferation of an organism make for excellent targets since exposure of bacteria to compounds active against these targets would result in the inactivation of the organism. Once a target is identified, biochemical analysis of that target can be used to discover or to design molecules that interact with and alter the functions of the target. Using physical and computational techniques, to analyze structural and biochemical targets in order to derive compounds that interact with a target is called rational drug design and offers great future potential. Thus, emerging drug discovery practices use molecular modeling techniques, combinatorial chemistry approaches, and other means to produce and screen and/or design large numbers of candidate compounds.

Nevertheless, while this approach to drug discovery is clearly the way of the future, problems remain. For example, the initial step of identifying molecular targets for investigation can be an extremely time consuming task. It may also be difficult to design molecules that interact with the target by using computer modeling techniques. Furthermore, in cases where the function of the target is not known or is poorly understood, it may be difficult to design assays to detect molecules that interact with and alter the functions of the target. To improve the rate of novel drug discovery and development, methods of identifying important molecular targets in pathogenic microorganisms and methods for identifying molecules that interact with and alter the functions of such molecular targets are urgently required.

Escherichia coli represents an excellent model system to understand bacterial biochemistry and physiology. The estimated 4288 genes scattered along the 4.6 x 10⁶ base pairs of the Escherichia coli (E. coli) chromosome offer tremendous promise for the understanding of bacterial biochemical processes. In turn, this knowledge will assist in the development of new tools for the diagnosis and treatment of bacteria-caused human disease. The entire E. coli genome has been sequenced, and this body of information holds a tremendous potential for application to the discovery and development of new antibiotic compounds. Yet, in spite of this accomplishment, the general functions or roles of many of these genes are still unknown. For example, the total number of proliferation-required genes contained within the E. coli genome is unknown, but has been variously estimated at around 200 to 700 (Armstrong, K.A. and Fan, D.P. Essential Genes in the metB-malB Region of Escherichia coli K12, 1975, J. Bacterial. 126: 48-55).

Novel, safe and effective antimicrobial compounds are needed in view of the rapid rise of antibiotic resistent microorganisms. However, prior to this invention, the characterization of even a single bacterial gene was a painstaking process, requiring years of effort. Accordingly, there is an urgent need for more novel methods to identify and characterize bacterial genomic sequences that encode gene products required for proliferation and for methods to identify molecules that interact with and alter the functions of such genes and gene products.

SUMMARY OF THE INVENTION

One embodiment of the present invention is a purified or isolated nucleic acid sequence consisting essentially of one of SEQ ID NOs: 1-81, 405-485, wherein said nucleic acid inhibits microorganism proliferation. The nucleic acid sequence may be complementary to at least a portion of a coding sequence of a gene whose expression is required for

microorganism proliferation. The nucleic acid sequence may comprise a fragment of one of SEQ ID NOs. 1-81, 405-485, said fragment selected from the group consisting of fragments comprising at least 10, at least 20, at least 25, at least 30, at least 50 or more than 50 consecutive bases of one of SEQ ID NOs: 1-81, 405-485. The nucleic acid sequence may be complementary to a coding sequence of a gene whose expression is required for microorganism proliferation.

Another embodiment of the present invention is a vector comprising a promoter operably linked to a nucleic acid comprising a sequence selected from the group consisting of SEO ID NOs. 1-81, 405-485. The promoter may be active in an organism selected from the group consisting of Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa, Enterobacter cloacae, Helicobacter pylori, Neisseria gonorrhoeae, Enterococcus faecalis, Streptococcus pneumoniae, Haemophilus influenzae, Salmonella typhimunum, Saccharomyces cerevisiae, Candida albicans, Cryptococcus neoformans, Aspergillus fumigatus, Klebsiella pneumoniae, Salmonella typhi, Salmonella paratyphi, Salmonella cholerasuis, Staphylococcus epidermidis, Mycobacterium tuberculosis, Mycobacterium leprae, Treponema pallidum, Bacillus anthracis, Yersinia pestis, Clostridium botulinum, campylobacter jejuni, Chlamydia trachomatus, Chlamydia pneumoniae or any species falling within the genera of any of the above species.

Another embodiment of the present invention is a host cell containing the vectors described above.

Another embodiment of the present invention is a purified or isolated nucleic acid consisting essentially of the coding sequence of one of SEQ ID NOs: 82-88, 90-242. One aspect of this embodiment is a fragment of the nucleic acid comprising at least 10, at least 20, at least 25, at least 30, at least 50 or more than 50 consecutive bases of one of SEQ ID NOs: 82-88, 90-242.

Another embodiment of the present invention is a vector comprising a promoter operably linked to the nucleic acids of the preceding embodiment.

Another aspect of the present invention is a purified or isolated nucleic acid comprising a nucleic acid sequence complementary to at least a portion of an intragenic sequence, intergenic sequence, sequences spanning at least a portion of two or more genes, 5' noncoding region, or 3' noncoding region within an operon encoding a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs: 243-357, 359-398.

Another embodiment of the present invention is a purified or isolated nucleic acid comprising a nucleic acid having at least 70% homology to a sequence selected from the group consisting of SEO ID NOs 1-81, 405-485, 82-88, 90-242 or the sequences complementary thereto as determined using BLASTN version 2.0 with the default parameters. The nucleic acid may be from an organism selected from the group consisting of Staphylococcus aureus, Pseudomonas aeruginosa, Enterobacter cloacae, Helicobacter pylori, Neissaria gonorrhoaae, Enterococcus taecalis, Streptococcus pneumoniae, Haemophilus influenzae, Salmonella typhimurium, Saccharomyces cerevisiae, Candida albicans, Cryptococcus neoformans, Aspergillus fumigatus, Klebsiella pneumoniae, Salmonella typhi, Salmonella paratyphi, Salmonella cholerasuis, Staphylococcus epidermidis, Mycobacterium tuberculosis, Mycobacterium teprae, Treponema pallidum, Bacillus anthracis, Yersinia pestis, Clostridium botulinum, campylobacter jejuni, and Chlamydia trachomatus, Chlamydia pneumoniae or any species falling within the genera of any of the above species.

Another embodiment of the present invention is a purified or isolated nucleic acid consisting essentially of a 5 nucleic acid encoding a polypeptide having a sequence selected from the group consisting of SEQ ID NOs.: 243-357, 359-398. Another embodiment of the present invention is a vector comprising a promoter operably linked to a nucleic acid encoding a polypeptide having a sequence selected from the group consisting of SEQ ID NDs.: 243-357, 359-398. 5 10 Another embodiment of the present invention is a host cell containing the vector of the preceding embodiment. Another embodiment of the present invention is purified or isolated polypeptide comprising the sequence of one of SEQ ID NOs: 243-357, 359-398. 15 Another embodiment of the present invention is purified or isolated polypeptide comprising a fragment of one 10 of the polypeptides of SEQ ID NDs. 243-357, 359-398, said fragment selected from the group consisting of fragments comprising at least 5, at least 10, at least 20, at least 30, at least 40, at least 50, at least 60 or more than 60 consecutive amino acids of one of the polypeptides of SEQ ID NOs.: 243-357, 359-398. 20 Another embodiment of the present invention is an antibody capable of specifically binding the polypeptide of 15 the preceding embodiment. Another embodiment of the present invention is method of producing a polypeptide, comprising introducing a vector comprising a promoter operably linked to a nucleic acid encoding a polypeptide having a sequence salected from 25 the group consisting of SEQ ID NOs. 243-357, 359-398into a cell. The method may further comprise the step of isolating said protein. Another embodiment of the present invention is a method of inhibiting proliferation comprising inhibiting the 20 activity or reducing the amount of a polypeptide having a sequence selected from the group consisting of SEQ ID NOs. 30 243-357, 359-398or inhibiting the activity or reducing the amount of a nucleic acid encoding said polypeptide. Another embodiment of the present invention is method for identifying compounds which influence the activity of a polypeptide required for proliferation comprising: 35 25 contacting a polypeptide comprising a sequence selected from the group consisting of 243-357, 359-398 with a candidate compound; and determining whether said compound influences the activity of said polypeptide. The activity may be an enzymatic activity. The activity may be a carbon compound catabolism activity. The 40 activity may be a biosynthetic activity. The activity may be a transporter activity. The activity may be a 30 transcriptional activity. The activity may be a DNA replication activity. The activity may be a cell division activity. Another embodiment of the present invention is a compound identified using the above method. Another embodiment of the present invention is method for assaying compounds for the ability to reduce the 45 activity or level of a polypeptide required for proliferation, comprising: providing a target, wherein said target comprises the coding sequence of a sequence selected from the group 35 consisting of SEO ID NOs. 82-88, 90-242;

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contacting said target with a candidate compound; and measuring an activity of said target.

The target may be a messenger RNA molecule transcribed from a coding region of one of SEQ ID. NOs.: 82-88, 90-242 and said activity is translation of said messenger RNA. The target may be a coding region of one of SEQ ID. NOs. 82-88, 90-242 and said activity is transcription of said messenger RNA.

Another embodiment of the present invention is a compound identified using the method above.

Another embodiment of the present invention is a method for identifying compounds which reduce the activity or level of a gene product required for cell proliferation comprising the steps of:

expressing an antisense nucleic acid against a nucleic acid encoding said gene product in a cell to reduce the activity or amount of said gene product in said cell, thereby producing a sensitized cell;

contacting said sensitized cell with a compound: and

determining whether said compound inhibits the growth of said sensitized cell to a greater extent than said compound inhibits the growth of a nonsensitized cell.

The cell may be selected from the group consisting of bacterial cells, fungal cells, plant cells, and animal cells. The cell may be an *E. coli* cell. The cell may be from an organism selected from the group consisting of *Staphylococcus aureus, Pseudomonas aeruginosa, Enterobacter cloacae, Helicobacter pylori, Neisseria gonorrhoeae, Enterococcus faecalis, Streptococcus pneumoniae, Haemophilus influenzae, Salmonella typhimurium, Saccharomyces cerevisiae, Candida albicans, Cryptococcus neoformans, Aspergillus fumigatus, Klebsiella pneumoniae, Salmonella typhi, Salmonella paratyphi, Salmonella cholerasuis, Staphylococcus epidermidis, Mycobacterium tuberculosis, Mycobacterium leprae, Treponema pallidum, Bacillus anthracis, Yersinia pestis, Clostridium botulinum, campylobacter jejuni, and Chlamydia trachomatus, Chlamydia pneumoniae or any species falling within the genera of any of the above species. The antisense nucleic acid may be transcribed from an inducible promoter. The method may, further comprise the step of contacting said cell with a concentration of inducer which induces said antisense nucleic acid to a sublethal level. The sub-lethal concentration of said inducer may be such that growth inhibition is 8% or more. The inducer may be isopropyl-1-thio-β-D-galactoside. The growth inhibition may be measured by monitoring optical density of a culture growth solution. The gene product may be a polypeptide. The gene product may be an RNA. The gene product may comprise a polypeptide having a sequence selected from the group consisting of SEO ID NOs.: 243-357, 359-398.*

Another embodiment of the present invention is a compound identified using the method above.

Another embodiment of the present invention is a method for inhibiting cellular proliferation comprising introducing a compound with activity against a gene corresponding to one of SEQ ID NOs.: 82-88, 90-242 or with activity against the product of said gene into a population of cells expressing a gene. The compound may be an antisense oligonucleatide comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-81, 405-485, or a proliferation-inhibiting portion thereof. The proliferation inhibiting portion of one of SEQ ID NOs. 1-81, 405-485

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may be a fragment comprising at least 10, at least 20, at least 25, at least 30, at least 50 or more than 50 consecutive bases of one of SEQ ID NOs: 1-81, 405-485. The compound may be a triple helix oligonucleotide.

Another embodiment of the present invention is a preparation comprising an effective concentration of an antisense oligonucleotide comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-81, 405-485, or a proliferation-inhibiting portion thereof in a pharmaceutically acceptable carrier. The proliferation-inhibiting portion of one of SEQ ID NOs. 1-81, 405-485 may comprise at least 10, at least 20, at least 25, at least 30, at least 50 or more than 50 consecutive bases of one of SEQ ID NOs: 1-81, 405-485.

Another embodiment of the present invention is a method for inhibiting the expression of a gene in an operon required for proliferation comprising contacting a cell in a cell population with an antisense nucleic acid, said cell expressing a gene corresponding to one of SEQ ID NOs.: 82-88, 90-242, wherein said antisense nucleic acid comprises at least a proliferation-inhibiting portion of said operon in an antisense orientation that is effective in inhibiting expression of said gene. The antisense nucleic acid may be complementary to a sequence of a gene comprising one or more of SEO ID NOs.: 82-88, 90-242. The antisense nucleic acid may be a sequence of one of SEO ID NOs.: 1-81, 405-485, or a portion thereof. The cell may be contacted with said antisense nucleic acid by introducing a plasmid which expresses said antisense nucleic acid into said cell population. The cell may be contacted with said antisense nucleic acid by introducing a phage which expresses said antisense nucleic acid into said cell population. The cell may be contacted with said antisense nucleic acid by introducing a sequence encoding said antisense nucleic acid into the chromosome of said cell into said cell population. The cell may be contacted with said antisense nucleic acid by introducing a retron which expresses said entisense nucleic acid into said cell population. The cell may be contacted with said antisense nucleic acid by introducing a ribozyme into said cell-population, wherein a binding portion of said ribozyme is complementary to said antisense oligonucleotide. The cell may be contacted with said antisense nucleic acid by introducing a liposome comprising said antisense oligonucleotide into said cell. The cell may be contacted with said antisense nucleic acid by electroporation. The antisense nucleic acid may be a fragment comprising at least 10, at least 20, at least 25, at least 30, at least 50 or more than 50 consecutive bases of one of SEO ID NOs: 82-88, 90-242. The antisense nucleic acid may be an oligonucleotide.

Another embodiment of the present invention is a method for identifying bacterial strains comprising the steps of:

providing a sample containing a bacterial species; and

identifying a bacterial species using a species specific probe having a sequence selected from the group consisting of SEQ ID NOs. 1-81, 405-485, 82-88, 90-242.

Another embodiment of the present invention is a method for identifying a gene in a microorganism required for proliferation comprising:

- (a) identifying an inhibitory nucleic acid which inhibits the activity of a gene or gene product required for proliferation in a first microorganism;
- (b) contacting a second microorganism with said inhibitory nucleic acid:

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		(c) determining whether said inhibitory nucleic acid from said first microorganism inhibits proliferation of said
5		second microorganism; and
		(d) identifying the gene in said second microorganism which is inhibited by said inhibitory nucleic acid.
		Another embodiment of the present invention is a method for assaying a compound for the ability to inhibit
40	5	proliferation of a microorganism comprising:
10		(a) identifying a gens or gene product required for proliferation in a first microorganism;
		(b) identifying a homolog of said gene or gene product in a second microorganism;
		(c) identifying an inhibitory nucleic acid sequence which inhibits the activity of said homolog in said second
15		microorgansim;
	10	(d) contacting said second microorganism with a proliferation-inhibiting amount of said inhibitory nucleic acid,
		thus sensitizing said second microorganism;
		(e) contacting the sensitized microorganism of step (d) with a compound; and
20		(f) determining whether said compound inhibits proliferation of said sensitized microorganism to a greater
		extent than said compound inhibits proliferation of a nonsensitized microorganism.
	15	The step of identifying a gene involved in proliferation in a first microorganism may comprise:
		introducing a nucleic acid comprising a random genomic fragment from said first microorganism operably
25		linked to a promoter wherein said random genomic fragment is in the antisense orientation; and
		comparing the proliferation of said first microorganism transcribing a first level of said random genomic
		fragment to the proliferation of said first microorganism transcribing a lower level of said random genomic fragment,
	20	wherein a difference in proliferation indicates that said random genomic fragment comprises a gene involved in
30		proliferation.
		The step of identifying a homolog of said gene in a second microorganism may comprise identifying a
		homologous nucleic acid or a nucleic acid encoding a homologous polypeptide in a database using an algorithm
1.		selected from the group consisting of BLASTN version 2.0 with the default parameters and FASTA version 3.0178
35	25	algorithm with the default parameters. The step of identifying a homolog of said gene in a second microorganism may
		comprise identifying a homologous nucleic acid or a nucleic acid encoding a homologous polypeptide by identifying
		nucleic acids which hybridize to said first gene. The step of identifying a homolog of said gene in a second
40		microorganism may comprise expressing a nucleic acid which inhibits the proliferation of said first microorganism in
40		said second microorganism. The inhibitory nucleic acid may be an antisense nucleic acid. The inhibitory nucleic acid
	30	may comprise an antisense nucleic acid to a portion of said homolog. The inhibitory nucleic acid may comprise an
		antisense nucleic acid to a portion of the operon encoding said homolog. The step of contacting the second
45		microorganism with a proliferation-inhibiting amount of said nucleic acid sequence may comprise directly contacting
		said second microorganism with said nucleic acid. The step of contacting the second microorganism with a
		proliferation-inhibiting amount of said nucleic acid sequence may comprise expressing an antisense nucleic acid to said
	35	homolog in said second microorganism.

Another embodiment of the present invention is a compound identified using the method above.

Another embodiment of the present invention is a method of assaying a compound for the ability to inhibit proliferation comprising:

- (a) identifying an inhibitory nucleic acid sequence which inhibits the activity of a gene or gene product required for proliferation in a first microorgansim;
- (b) contacting a second microorganism with a proliferation-inhibiting amount of said inhibitory nucleic acid, thus sensitizing said second microorganism;
- (c) contacting the proliferation-inhibited microorganism of step (b) with a compound; and
- (d) determining whether said compound inhibits proliferation of said sensitized second microorganism to a greater extent than said compound inhibits proliferation of a nonsensitized second microorganism.

The inhibitory nucleic acid may be an antisense nucleic acid which inhibits the proliferation of said first microorganism. The inhibitory nucleic acid may comprise a portion of an antisense nucleic acid which inhibits the proliferation of said first microorganism. The inhibitory nucleic acid may comprise an antisense molecule against the entire coding region of the gene involved in proliferation of the first microorganism. The inhibitory nucleic acid may comprise an antisense nucleic acid to a portion of the operon encoding the gene involved in proliferation of the first microorganism.

Another embodiment of the present invention is a compound identified using the method above.

Another embodiment of the present invention is a method for assaying compounds for activity against a biological pathway required for proliferation comprising:

sensitizing a call by expressing an antisense nucleic acid against a nucleic acid encoding a gene product required for proliferation in a cell to reduce the activity or amount of said gene product;

contacting the sensitized cell with a compound; and

determining whether said compound inhibits the growth of said sensitized cell to a greater extent than said compound inhibits the growth of an nonsensitized cell.

The cell may be selected from the group consisting of bacterial cells, fungal cells, plant cells, and animal cells. The cell may be an E. coli cell. The cell may be an organism selected from the group consisting of Staphylococcus aureus, Pseudomonas aeruginosa, Enterobacter cloacae, Helicobacter pylori, Neisseria gonorrhoeae, Enterococcus faecalis, Streptococcus pneumoniae, Haemophilus influenzae, Salmonella typhimurium, Saccharomyces cerevisiae, Candida albicans, Cryptococcus neoformans, Aspergillus fumigatus, Klebsiella pneumoniae, Salmonella typhi, Salmonella paratyphi, Salmonella cholerasuis, Staphylococcus epidermidis, Mycobacterium tuberculosis, Mycobacterium leprae, Treponema pallidum, Bacillus anthracis, Yersinia pestis, Clostridium botulinum, campylobacter jejuni, and Chlamydia trachomatus, Chlamydia pneumoniae or any species falling within the genera of any of the above species. The antisense nucleic acid may be transcribed from an inducible promoter. The method may further comprise contacting the cell with an agent which induces expression of said antisense nucleic acid from said inducible promoter, wherein said antisense nucleic acid is expressed at a sublethal level. The sublethal level of said antisense nucleic acid

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may inhibit proliferation by 8% or more. The agent may be isopropyl-1-thio-β-D-galactoside (IPTG). The inhibition of 5 proliferation may be measured by monitoring the optical density of a liquid culture. The gene product may comprise a polypeptide having a sequence selected from the group consisting of SEO ID NOs: 243-357, 359-398. Another embodiment of the present invention is a compound identified using the method above. Another embodiment of the present invention is a method for assaying a compound for the ability to inhibit 5 10 cellular proliferation comprising: contacting a cell with an agent which reduces the activity or level of a gene product required for proliferation of said cell; contacting said cell with said compound; and 15 10 determining whether said compound reduces proliferation to a greater extent than said compound reduces proliferation of cells which have not been contacted with said agent. The agent which reduces the activity or level of a gene product required for proliferation of said cell may comprise an antisense nucleic acid to a gene or operon required for proliferation. The agent which reduces the activity 20 or level of a gene product required for proliferation of said cell may comprise an antibiotic. The cell may contain a temperature sensitive mutation which reduces the activity or level of said gene product required for proliferation of 15 said cell. The antisense nucleic acid may be directed against the same functional domain of said gene product required for proliferation of said cell to which said antisense nucleic acid is directed. The antisense nucleic acid may be directed 25 against a different functional domain of said gene product required for proliferation of said cell than the fucntional domain to which said antisense nucleic acid is directed. 20 Another embodiment of the present invention is a compound identified using the method above. Another embodiment of the present invention is a method for identifying the pathway in which a 30 proliferation-required nucleic acid or its gane product lies comprising: expressing a sublethal level of an antisense nucleic acid directed against said proliferation-required nucleic acid in a cell; 35 25 contacting said cell with an antibiotic, wherein the a biological pathway on which said antibiotic acts is known; and determining whether said cell has a substantially greater sensitivity to said antibiotic than a cell which does not express said sublethal level of said antisense nucleic acid. 40 Another embodiment of the present invention is a method for determining the pathway on which a test 30 compound acts comprising: (a) expressing a sublethal level of an antisense nucleic acid directed against a proliferation-required nucleic acid in a cell, wherein the biological pathway in which said proliferation-required nucleic acid lies is known, 45 (b) contacting said cell with said test compound; and (c) determining whether said cell has a substantially greater sensitivity to said test compound than a cell

which does not express said sublethal level of said antisense nucleic acid.

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The method may further comprise: 5 (d) expressing a sublethal level of a second entisense nucleic acid directed against a second proliferation-required nucleic acid in said cell, wherein said second proliferation-required nucleic acid is in a different biological pathway than said proliferation-required nucleic acid in step (a); and 5 (e) determining whether said cell has a substantially greater sensitivity to said test compound than a cell which does 10 not express said sublethal level of said second antisense nucleic acid. Another embodiment of the present invention is a purified or isolated nucleic acid consisting essentially of one of SEO ID NOs: 358, 399-402. Another embodiment of the present invention is a purified or isolated nucleic acid comprising a sequence 15 10 selected from the group consisting of 1-81, 405-485, 82-88, 90-242, 358, 399-402. Another embodiment of the present invention is a compound which interacts with the gene or gene product of a nucleic acid comprising a sequence of one of SEQ ID NOs: 82-88, 90-242 to inhibit proliferation. Another embodiment of the present invention compound which interacts with a polypeptide comprising one 20 of SEQ ID NOs. 243-357, 359-398 to inhibit proliferation. Another embodiment of the present invention is a compound which interacts with a nucleic acid comprising 15 one of SEO ID NOs: 358, 399-402 to inhibit proliferation. 25 **BRIEF DESCRIPTION OF THE DRAWINGS** Figure 1 is an IPTG dose response curve in E. coli transformed with an IPTG-inducible plasmid containing either an antisense clone to the E. coli ribosomal protein rpIW (AS-rpIW) which is required for protein 20 synthesis and essential cell proliferation, or an antisense clone to the elaD (AS-elaD) gene which is not known to be 30 involved in protein synthesis and which is also essential for proliferation. Figure 2A is a tetracycline dose response curve in E. coli transformed with an IPTG-inducible plasmid containing antisense to rplW(AS-rplW) in the presence of 0, 20 or 50 μM IPTG. Figure 2B is a tetracycline dose response curve in *E. coli* transformed with an IPTG-inducible 35 25 plasmid containing antisense to elaD (AS-elaD) in the presence of 0, 20 or 50 μ M IPTG. Figure 3 is a graph showing the fold increase in tetracycline sensitivity of E. coli transfected with antisense clones to essential ribosomal proteins L23 (AS-rpIW) and L7/L12 and L10 (AS-rpILrpLJ). Antisense clones to genes known not to be involved in protein synthesis (atpB/E(AS-atpB/E), visC (AS-visC, elaD (AS-elaD), yohH (AS-40 yohH) are much less sensitive to tetracycline. 30 <u>Definitions</u>

By "biological pathway" is meant any discrete cell function or process that is carried out by a gene product or a subset of gene products. Biological pathways include enzymatic, biochemical and metabolic pathways as well as pathways involved in the production of cellular structures such cell walls. Biological pathways that are usually required for proliferation of microorganisms include, but are not limited to, cell division, DNA synthesis & replication,

RNA synthesis (transcription), protein synthesis (translation), protein processing, protein transport, fatty acid biosynthesis, cell wall synthesis, cell membrane synthesis & maintenance, etc.

By "inhibit activity against a gene or gene product" is meant having the ability to interfere with the function of a gene or gene product in such a way as to decrease expression of the gene or to reduce the level or activity of a product of the gene. Agents which have activity against a gene include agents that inhibit transcription of the gene and agents that inhibit translation of the mRNA transcribed from the gene. In microorganisms, agents which have activity against a gene can act to decrease expression of the operon in which the gene resides or alter the processing of operon RNA such as to reduce the level or activity of the gene product. The gene product can be a non-translated RNA such as ribosomal RNA, a translated RNA (mRNA) or the protein product resulting from translation of the gene mRNA. Of particular utility to the present invention are anti-sense RNAs that have activities against the operons or genes to which they specifically hybridze.

By "activity against a gene product" is meant having the ability to inhibit the function or to reduce the level or activity of the gene product in a cell.

By "activity against a protein" is meant having the ability to inhibit the function or to reduce the level or activity of the protein in a cell.

By "activity against nucleic acid" is meant having the ability to inhibit the function or to reduce the level or activity of the nucleic acid in a cell.

As used herein, "sublethal" means a concentration of an agent below the concentration required to inhibit all cell growth.

DETAILED DESCRIPTION OF THE INVENTION

The present invention describes a group of *E. coli* genes and gene families required for growth and/or proliferation. A proliferation-required gene or gene family is one where, in the absence of a gene transcript and/or gene product, growth or viability of the microorganism is reduced or eliminated. Thus, as used herein the terminology "proliferation-required" or "required for proliferation" encompasses sequences where the absence of a gene transcript and/or gene product completely eliminates cell growth as well as sequences where the absence of a gene transcript and/or gene product merely reduces cell growth. These proliferation-required genes can be used as potential targets for the generation of new antimicrobial agents. To achieve that goal, the present invention also encompasses novel assays for analyzing proliferation-required genes and for identifying compounds which interact with the gene products of the proliferation-required genes. In addition, the present invention contemplates the expression of genes and the purification of the proteins encoded by the nucleic acid sequences identified as required proliferation genes and reported herein. The purified proteins can be used to generate reagents and screen small molecule libraries or other candidate compound libraries for compounds that can be further developed to yield novel antimicrobial compounds. The present invention also describes methods for identification of homologous genes in organisms other than *E. coli*.

The present invention utilizes a novel method to identify proliferation-required *E. coli* sequences. Generally, a library of nucleic acid sequences from a given source are subcloned or otherwise inserted into an inducible expression

vector, thus forming a organism into which to the insert nucleic acidefined as the product defined as the product also be used to refer which a ribonucleic acide the expression vector message expressed for vector can produce and ultimately translated in Once general

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vector, thus forming an expression library. Although the insert nucleic acids may be derived from the chromosome of the organism into which the expression vector is to be introduced, because the insert is not in its natural chromosomal location, the insert nucleic acid is an exogenous nucleic acid for the purposes of the discussion herein. The term expression is defined as the production of an RNA molecule from a gene, gene fragment, genomic fragment, or operon. Expression can also be used to refer to the process of peptide or polypeptide synthesis. An expression vector is defined as a vehicle by which a ribonucleic acid (RNA) sequence is transcribed from a nucleic acid sequence carried within the expression vehicle. The expression vector can also contain features that permit translation of a protein product from the transcribed RNA message expressed from the exogenous nucleic acid sequence carried by the expression vector. Accordingly, an expression vector can produce an RNA molecule as its sole product or the expression vector can produce a RNA molecule that is ultimately translated into a protein product.

Once generated, the expression library containing the exogenous nucleic acid sequences is introduced into an *E. coli* population to search for genes that are required for bacterial proliferation. Because the library molecules are foreign to the population of *E. coli*, the expression vectors and the nucleic acid segments contained therein are considered exogenous nucleic acid.

Expression of the exogenous nucleic acid fragments in the test population of *E. coli* containing the expression vector library is then activated. Activation of the expression vectors consists of subjecting the cells containing the vectors to conditions that result in the expression of the exogenous nucleic acid sequences carried by the expression vector library. The test population of *E. coli* cells is then assayed to determine the effect of expressing the exogenous nucleic acid fragments on the test population of cells. Those expression vectors that, upon activation and expression, negatively impact the growth of the *E. coli* screen population were identified, isolated, and purified for further study.

A variety of assays are contemplated to identify nucleic acid sequences that negatively impact growth upon expression. In one embodiment, growth in *E. coli* cultures expressing exogenous nucleic acid sequences and growth in cultures not expressing these sequences is compared. Growth measurements are assayed by examining the extent of growth by measuring optical densities. Alternatively, enzymatic assays can be used to measure bacterial growth rates to identify exogenous nucleic acid sequences of interest. Colony size, colony morphology, and cell morphology are additional factors used to evaluate growth of the host cells. Those cultures that failed to grow or grow with reduced efficiency under expression conditions are identified as containing an expression vector encoding a nucleic acid fragment that negatively affects a proliferation-required gene.

Once exogenous nucleic acid sequences of interest are identified, they are analyzed. The first step of the analysis is to acquire the nucleic acid sequence of the nucleic acid fragment of interest. To achieve this end, the insert in those expression vectors identified as containing a sequence of interest is sequenced, using standard techniques well known in the art. The next step of the process is to determine the source of the nucleic acid sequence.

Determination of sequence source is achieved by comparing the obtained sequence data with known sequences in various genetic databases. The sequences identified are used to probe these gene databases. The result of this

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procedure is a list of exogenous nucleic acid sequences corresponding to a list that includeds novel bacterial genes required for proliferation as well as genes previously identified as required for proliferation.

The number of DNA and protein sequences available in database systems has been growing exponentially for years. For example, at the end of 1998, the complete sequences of Caenorhabditis elegans, Seccharomyces cerevisiae and nineteen bacterial genomes, including E. coli were available. This sequence information is stored in a number of databanks, such as GenBank (the National Center for Biotechnology Information (NCBI), and is publicly available for searching.

A variety of computer programs are available to assist in the analysis of the sequences stored within these databases. FastA, (W. R. Pearson (1990) "Rapid and Sensitive Sequence Comparison with FASTP and FASTA" Methods in Enzymology 183:63- 98), Sequence Retrieval System (SRS), (Etzold & Argos, SRS an indexing and retrieval tool for flat file data libraries. Comput. Appl. Biosci. 9:49-57, 1993) are two examples of computer programs that can be used to analyze sequences of interest. In one embodiment of the present invention, the BLAST family of computer programs, which includes BLASTN version 2.0 with the default parameters, or BLASTX version 2.0 with the default parameters, is used to analyze nucleic acid sequences.

BLAST, an acronym for "Basic Local Alignment Search Tool," is a family of programs for database similarity searching. The BLAST family of programs includes: BLASTN, a nucleotide sequence database searching program, BLASTX, a protein database searching program where the input is a nucleic acid sequence; and BLASTP, a protein database searching program. BLAST programs embody a fast algorithm for sequence matching, rigorous statistical methods for judging the significance of matches, and various options for tailoring the program for special situations. Assistance in using the program can be obtained by e-mail at blast@ncbi.nlm.nih.gov.

Bacterial genes are often transcribed in polycistronic groups. These groups comprise operons, which are a collection of genes and intergenic sequences. The genes of an operon are co-transcribed and are often related functionally. Given the nature of the screening protocol, it is possible that the identified exogenous nucleic acid sequence corresponds to a gene or portion thereof with or without adjacent noncoding sequences, an intragenic sequence (i.e. a sequence within a gene), an intergenic sequence (i.e. a sequence between genes), a sequence spanning at least a portion of two or more genes, a 5' noncoding region or a 3' noncoding region located upstream or downstream from the actual sequence that is required for bacterial proliferation. Accordingly, determining which of the genes that are encoded within the operons are individually required for proliferation is often desirable.

In one embodiment of the present invention, an operon is dissected to determine which gene or genes are required for proliferation. For example, the RegulonOB DataBase described by Huerta et al. Wucl. Acids Res. 28:55-59, 1998), which may also be found on the website http://www.cifn.unam.mx/Computational_Biology/regulondb/, may be used. to identify the boundaries of operons encoded within microbial genomes. A number of techniques that are well known in the art can be used to dissect the operon. In one aspect of this embodiment, gene disruption by homologous recombination is used to individually inactivate the genes of an operon that is thought to contain a gene required for proliferation.

Several gene disruption techniques have been described for the replacement of a functional gene with a mutated, non-functional (null) allele. These techniques generally involve the use of homologous recombination. The

method described by Link et al. (J. Bacteriol 1997 179:6228; incorporated herein by reference in it's entirety) serves as an excellent example of these methods as applicable to disruption of genes in *E. cali*. This technique uses crossover PCR to create a null allele with an in-frame deletion of the coding region of a target gene. The null allele is constructed in such a way that sequences adjacent to the wild type gene (ca. 500 bp) are retained. These homologous sequences surrounding the deletion null allele provide targets for homologous recombination so that the wild type gene on the *E. coli* chromosome can be replaced by the constructed null allele.

The crossover PCR amplification product is subcloned into the vector pK03, the features of which include a chloramphenical resistance gene, the counter-selectable marker sacB, and a temperature sensitive autonomous replication function. Following transformation of an E. coli cell population with such a vector, selection for cells that have undergone homologous recombination of the vector into the chromosome is achieved by growth on chloramphenical at the non-permissive temperature of 43°C. Under these conditions, autonomous replication of the plasmid cannot occur and cell are resistant to chloramphinical only if the chloramphenical resistance gene has been integrated into the chromosome. Usually a single crossover event is responsible for this integration event such that the E. coli chromosome now contains a tandem duplication of the target gene consisting of one wild type allele and one deletion null allele separated by vector sequence.

This new *E. coli* strain containing the tandem duplication can be maintained at permissive temperatures in the presence of drug selection (chloramphenicol). Subsequently, cells of this new strain are cultured at the permissive temperature 30°C without drug selection. Under these conditions, the chromosome of some of the cells within the population will have undergone an internal homologous recombination event resulting in removal of the plasmid sequences. Subsequent culturing of the strain in growth medium lacking chloramphenicol but containing sucrose is used to select for such recombinative resolutions. In the presence of the counter-selectable marker *sacB*, sucrose is rendered into a toxic metabolite. Thus, cells that survive this counter-selection have lost both the plasmid sequences from the chromosome and the autonomously replicating plasmid that results as a byproduct of recombinative resolution.

There are two possible outcomes of the above recombinative resolution via homologous recombination. Either the wild type copy of the targeted gene is retained on the chromosome or the mutated null allele is retained on the chromosome. In the case of an essential gene, a single copy of the null allele would be lethal and such cells should not be obtained by the above procedure when applied to essential genes. In the case of a non-essential gene, roughly equal numbers of cells containing null alleles and cells containing wild type alleles should be obtained. Thus, the method serves as a test for essentiality of the targeted gene: when applied to essential genes, only cells with a wild type allele on the chromosome will be obtained.

Other techniques have also been described for the creation of disruption mutations in *E. coli*. For example, Link et al. also describe inserting an in-frame sequence tag concommitantly with an in-frame delation in order to simplify analysis of recombinants obtained. Further, Link et al. describe disruption of genes with a drug resistance marker such as a kanamycin resistance gene. Arigoni et al., (Arigoni, F. et al. A Gename-based Approach for the

Identification of Essential Bacterial Genes, Nature Biotechnology 16: 851-856, the disclosure of which is incorporated herein by reference in its entirety) describe the use of gene disruption combined with engineering a second copy of a test gene such that the expression of the gene is regulated by and inducible promoter such as the arabinose promoter to test the essentiality of the gene. Many of these techniques result in the insertion of large fragments of DNA into the gene of interest, such as a drug selection marker. An advantage of the technique described by Link et al. is that it does not rely on an insertion into the gene to cause a functional defect, but rather results in the precise removal of the coding region. This insures the lack of polar effects on the expression of genes downstream from the target gene.

Recombinant DNA techniques can be used to express the entire coding sequences of the gene identified as required for profiferation, or portions thereof. The over-expressed proteins can be used as reagents for further study. The identified exogenous sequences are isolated, purified, and cloned into a suitable expression vector using methods well known in the art. If desired, the nucleic acids can contain the sequences encoding a signal peptide to facilitate secretion of the expressed protein.

Expression of fragments of the bacterial genes identified as required for proliferation is also contemplated by the present invention. The fragments of the identified genes can encode a polypeptide comprising at least 5, at least 10, at least 15, at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, at least 50, at least 55, at least 60, at least 85, at least 75, or more than 75 consecutive amino acids of a gene complementary to one of the identified sequences of the present invention. The nucleic acids inserted into the expression vectors can also contain sequences upstream and downstream of the coding sequence.

When expressing the coding sequence of an entire gene identified as required for bacterial proliferation or a fragment thereof, the nucleic acid sequence to be expressed is operably linked to a promoter in an expression vector using conventional cloning technology. The expression vector can be any of the bacterial, insect, yeast, or mammalian expression systems known in the art. Commercially available vectors and expression systems are available from a variety of suppliers including Genetics Institute (Cambridge, MA), Stratagene (La Jolla, California), Promega (Madison, Wisconsin), and Invitrogen (San Diego, California). If desired, to enhance expression and facilitate proper protein folding, the codon usage and codon bias of the sequence can be optimized for the particular expression organism in which the expression vector is introduced, as explained by Hatfield, et al., U.S. Patent No. 5,082,767, incorporated herein by this reference. Fusion protein expression systems are also contemplated by the present invention.

Following expression of the protein encoded by the identified exogenous nucleic acid sequence, the protein is purified. Protein purification techniques are well known in the art. Proteins encoded and expressed from identified exogenous nucleic acid sequences can be partially purified using precipitation techniques, such as precipitation with polyethylene glycol. Chromatographic methods usable with the present invention can include ion-exchange chromatography, gel filtration, use of hydroxyapaptite columns, immobilized reactive dyes, chromatofocusing, and use of high-performance liquid chromatography. Electrophoretic methods such one-dimensional gel electrophoresis, high-resolution two-dimensional polyacrylamide electrophoresis, isoelectric focusing, and others are contemplated as purification methods.

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Also, affinity chromatographic methods, comprising antibody columns, ligand presenting columns and other affinity chromatographic matrices are contemplated as purification methods in the present invention.

The purified proteins produced from the gene coding sequences identified as required for proliferation can be used in a variety of protocols to generate useful antimicrobial reagents. In one embodiment of the present invention, antibodies are generated against the proteins expressed from the identified exogenous nucleic acid sequences. Both monoclonal and polycional antibodies can be generated against the expressed proteins. Methods for generating monocional and polycional antibodies are well known in the art. Also, antibody fragment preparations prepared from the produced antibodies discussed above are contemplated.

Another application for the purified proteins of the present invention is to screen small molecule libraries for candidate compounds active against the various target proteins of the present invention. Advances in the field of combinatorial chemistry provide methods, well known in the art, to produce large numbers of candidate compounds that can have a binding, or otherwise inhibitory effect on a target protein. Accordingly, the screening of small molecule libraries for compounds with binding affinity or inhibitory activity for a target protein produced from an identified gene sequence is contemplated by the present invention.

The present invention further contemplates utility against a variety of other pathogenic organisms in addition to E. coli. For example, the invention has utility in identifying genes required for proliferation in prokaryotes and eukaryotes. For example, the invention has utility with protists, such as Plasmodium spp.; plants; animals, such as Entamoeba spp. end Contracaecum spp; and fungi including Candida spp., (e.g., Candida albicans), Saccharomyces cerevisiae, Cryptococcus neoformans, and Aspergillus fumigatus. In one embodiment of the present invention, monera, specifically bacteria are probed in search of novel gene sequences required for proliferation. This embodiment is particularly important given the rise of drug resistant bacteria.

The numbers of bacterial species that are becoming resistant to existing antibiotics are growing. A partial list of these organisms includes: Staphylococcus spp., such as S. aureus; Enterococcus spp., such as E. faecalis; Pseudomonas spp., such as P. aeruginosa, Clostridium spp., such as C. botulinum, Haemophilus spp., such as H. influenzae, Enterobacter spp., such as E. cloacae, Vibrio spp., such as V. cholera; Moraxala spp., such as M. catarrhalis; Streptococcus spp., such as S. pneumoniae, Neisseria spp., such as N. gonorrhoeae; Mycoplasma spp., such as Mycoplasma pneumoniae; Salmonella typhimurium; Helicobacter pylori; Escherichia coli; and Mycobacterium tuberculosis: The sequences identified as required for proliferation in the present invention can be used to probe these and other organisms to identify homologous required proliferation genes contained therein.

In one embodiment of the present invention, the nucleic acid sequences disclosed herein are used to screen genomic libraries generated from bacterial species of interest other than E. coli. For example, the genomic library may be from Staphylococcus aureus, Psaudomonas aeruginosa, Enterobacter cloacaa, Helicobacter pylori, Neisseria gonorrhoese, Enterococcus faecalis, Streptococcus pneumoniae, Haemophilus influenzae, Salmonella typhimurium, Saccharomycas cerevisiae, Candida albicans, Cryptococcus naoformans, Aspergillus fumigatus, Klabsiella pneumoniaa, Salmonella typhi, Salmonella paratyphi, Salmonella cholarasuis, Staphylococcus epidarmidis, Mycobacterium

tuberculosis, Mycobacterium lepree, Treponeme pallidum, Bacillus anthracis, Yersinia pestis, Clostridium botulinum, Campylobacter jejuni, Chlemydia trachomatus, Chlemydia pneumoniae or any species falling within the genera of any of the above species. Standard molecular biology techniques are used to generate genomic libraries from various microorganisms. In one aspect, the libraries are generated and bound to nitrocellulose paper. The identified exogenous nucleic acid sequences of the present invention can then be used as probes to screen the libraries for homologous sequences. The homologous sequences identified can then be used as targets for the identification of new, antimicrobial compounds with activity against more than one organism.

For example, the preceding methods may be used to isolate nucleic acids having a sequence with at least 97%, at least 95%, at least 80%, at least 80%, or at least 70% identity to a nucleic acid sequence selected from the group consisting of one of the sequences of SEQ ID NOS. 1-81, 405-485, 82-88, 90-242, fragments comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive bases thereof, and the sequences complementary thereto. Identity may be measured using BLASTN version 2.0 with the default parameters. (Altschul, S.F. et al. Gapped BLAST and PSI-BLAST: A New Generation of Protein Database Search Programs, Nucleic Acid Res. 25: 3389-3402 (1997), the disclosure of which is incorporated herein by reference in its entirety). For example, the homologous polynucleotides may have a coding sequence which is a naturally occurring allelic variant of one of the coding sequences described herein. Such allelic variants may have a substitution, deletion or addition of one or more nucleotides when compared to the nucleic acids of SEQ ID NOs: 1-81, 405-485, 82-88, 90-242 or the sequences complementary thereto.

Additionally, the above procedures may be used to isolate nucleic acids which encode polypeptides having at least 99%, 95%, at least 90%, at least 85%, at least 80%, at least 70%, at least 60%, at least 50%, or at least 40% identity or similarity to a polypeptide having the sequence of one of SEO ID NOs: 243-357, 359-398or fragments comprising at least 5, 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, or 150 consecutive amino acids thereof as determined using the FASTA version 3.0t78-algorithm with the default parameters. Alternatively, protein identity or similarity may be identified using BLASTP with the default parameters, BLASTX with the default parameters, or TBLASTN with the default parameters. (Alschul, S.F. et al. Gapped BLAST and PSI-BLAST: A New Generation of Protein Database Search Programs, Nucleic Acid Res. 25: 3389-3402 (1997), the disclosure of which is incorporated herein by reference in its entirety).

Alternatively, homologous nucleic acids or polypeptides may be identified by searching a database to identify sequences having a desired level of homology to a nucleic acid or polypeptide involved in proliferation or an antisense nucleic acid to a nucleic acid involved in microbial proliferation. A variety of such databases are available to those skilled in the art, including GenBank and GenSeq. In some embodiments, the databases are screened to identify nucleic acids or polypeptides having at least 97%, at least 95%, at least 90%, at least 85%, at least 80%, at least 70%, at least 60%, or at least 50%, at least 40% identity or similarity to a nucleic acid or polypeptide involved in proliferation or an antisense nucleic acid involved in proliferation. For example, the database may be screened to identify nucleic acids homologous to one of SEQ ID Nos. 1-81, 405-485, 82-88, 90-242 or polypeptides homologous

to SEO ID NOs. 243-357, 359-398. In some embodiments, the database may be screened to identify homologous nucleic acids or polypeptides from organisms other than *E. coli*, including organisms such as *Staphylococcus auraus*, *Psaudomonas aeruginosa*, *Enterobacter cloacae*, *Halicobacter pylori*, *Neisseria gonorrhoaae*, *Enterococcus faecelis*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Salmonella typhimurium*, *Saccharomycas ceravisiae*, *Candida albicans*, *Cryptococcus neoformans*, *Aspergillus fumigatus*, *Klebsiella pneumoniae*, *Salmonella typhi*, *Salmonella paratyphi*, *Salmonella cholerasuis*, *Staphylococcus epidermidis*, *Mycobacterium tubarculosis*, *Mycobacterium leprae*, *Treponema pallidum*, *Bacillus anthracis*, *Yersinia pestis*, *Clostridium botulinum*, *Campylobacter jejuni*, *Chlamydia pneumoniae* or any species falling within the genera of any of the above species.

In another embodiment, gene expression arrays and microarrays can be employed. Gene expression arrays are high density arrays of DNA samples deposited at specific locations on a glass chip, nylon membrana, or the fike. Such arrays can be used by researchers to quantify relative gene expression under different conditions. Gene expression arrays are used by researchers to help identify optimal drug targets, profile new compounds, and determine disease pathways. An example of this technology is found in U.S. Patent No. 5807522, which is hereby incorporated by reference.

It is possible to study the expression of all genes in the genome of a particular microbial organism using a single array. For example, the arrays from Genosys consist of 12 x 24 cm nylon filters containing PCR products corresponding to 4290 ORFs from *E. coli.* 10 ngs of each are spotted every 1.5 mm on the filter. Single stranded labeled cDNAs are prepared for hybridization to the array (no second strand synthesis or emplification step is done) and placed in contact with the filter. Thus the labeled cDNAs are of "antisense" orientation. Quantitative analysis is done by phosphorimager.

Hybridization of cDNA made from a sample of total cell mRNA to such an array followed by detection of binding by one or more of various techniques known to those in the art results in a signal at each location on the array to which cDNA hybridized. The intensity of the hybridization signal obtained at each location in the array thus reflects the amount of mRNA for that specific gene that was present in the sample. Comparing the results obtained for mRNA isolated from cells grown under different conditions thus allows for a comparison of the relative amount of expression of each individual gene during growth under the different conditions.

Gene expression arrays may be used to analyze the total mRNA expression pattern at various time points after induction of an antisense nucleic acid against a proliferation-required gene. Analysis of the expression pattern indicated by hybridization to the array provides information on whether or not the target gene of the antisense nucleic acid is being affected by antisense induction, how quickly the antisense is affecting the target gene, and for later timepoints, what other genes are affected by antisense expression. For example, if the antisense is directed against a gene for ribosomal protein L7/L12 in the 50S subunit, its targeted mRNA may disappear first and then other mRNAs may be observed to increase, decrease or stay the same. Similarly, if the antisense is directed against a different 50S subunit ribosomal protein mRNA (e.g. 125), that mRNA may disappear first followed by changes in mRNA expression that are similar to those seen with the L7/L12 antisense expression. Thus, the mRNA expression pattern observed

with an antinsense nucleic acid against a proliferation required gene may identify other proliferation-required nucleic acids in the same pathway as the target of the antisense nucleic acid. In addition, the mRNA exprassion patterns observed with candidate drug compounds may be compared to those observed with antisense nucleic acids against a proliferation-required nucleic acid. If the mRNA expression pattern observed with the candidate drug compound is similar to that observed with the antisense nucleic acid, the drug compound may be a promising therapeutic candidate. Thus, the assay would be useful in assisting in the selection of candidate drug compounds for use in screening methods such as those described below.

In cases where the source of nucleic acid deposited on the array and the source of the nucleic acid being hybridized to the array are from two different organisms, gene expression arrays can identify homologous genes in the two organisms.

The present invention also contemplates additional methods for screening other microorganisms for proliferation-required genes. In this embodiment, the conserved portions of sequences identified as proliferation-required can be used to generate degenerate primers for use in the polymerase chain reaction (PCR). The PCR technique is well known in the art. The successful production of a PCR product using degenerate probes generated from the sequences identified herein would indicate the presence of a homologous gene sequence in the species being screened. This homologous gene is then isolated, expressed, and used as a target for candidate antibiotic compounds. In another aspect of this embodiment, the homologous gene is expressed in an autologous organism or in a heterologous organism in such a way as to alter the level or activity of a homologous gene required for proliferation in the autologous or heterologous organism. In still another aspect of this embodiment, the homologous gene or portion is expressed in an antisense orientation in such a way as to alter the level or activity of a nucleic acid required for proliferation of an autologous or heterologous organism.

The homologous sequences to proliferation-required genes identified using the techniques described herein may be used to identify proliferation-required genes of organisms other than *E. coli*, to inhibit the proliferation of organisms other than *E. coli* by inhibiting the activity or reducing the amount of the identified homologous nucleic acid or polypeptide in the organism other than *E. coli*, or to identify compounds which inhibit the growth of organisms other than E. coli as described below.

In another embodiment of the present invention, $E.\ coli$ sequences identified as required for proliferation are transferred to expression vectors capable of function within non- $E.\ coli$ species. As would be appreciated by one of ordinary skill in the art, expression vectors must contain certain elements that are species specific. These elements can include promoter sequences, operator sequences, repressor genes, origins of replication, ribosomal binding sequences, termination sequences, and others. To use the identified exogenous sequences of the present invention, one of ordinary skill in the art would know to use standard molecular biology techniques to isolate vectors containing the sequences of interest from cultured bacterial cells, isolate and purify those sequences, and subclone those sequences into an expression vector adapted for use in the species of bacteria to be screened.

Expression vectors for a variety of other species are known in the art. For example, Cao et al. report the expression of steroid receptor fragments in Staphylococcus aureus. J. Steroid Biochem Mol Biol. 44(1):1-11

(1993). Also, Pla et al. have reported an expression vector that is functional in a number of relevant hosts including: Salmonelle typhimurium, Pseudomonas putida, and Pseudomonas aeruginosa. J. Bacteriol. 172(8):4448-55 (1990). These examples demonstrate the existence of molecular biology techniques capable of constructing expression vectors for the species of bacteria of interest to the present invention.

Following the subcloning of the identified nucleic acid sequences into an expression vector functional in the microorganism of interest, the identified nucleic acid sequences are conditionally transcribed to assay for bacterial growth inhibition. Those expression vectors found to contain sequences that, when transcribed, inhibit bacterial growth are compared to the known genomic sequence of the pathogenic microorganism being screened or, if the homologous sequence from the organism being screened is not known, it may be identified and isolated by hybridization to the proliferation-required £. coli sequence interest or by amplification using primers based on the proliferation-required £. coli sequence of interest as described above.

The antisense sequences from the second organism which are identified as described above may then be operably linked to a promoter, such as an inducible promoter, and introduced into the second organism. The techniques described herein for identifying *E. coli* genes required for proliferation may thus be employed to determine whether the identified sequences from a second organism inhibit the proliferation of the second organism.

Antisense nucleic acids required for the proliferation of organisms other than *E. coli* or the genes corresponding thereto, may also be hybridized to a microarray containing the *E. coli* ORFs to gauge the homology between the *E. coli* sequences and the proliferation-required nucleic acids from other organisms. For example, the proliferation-required nucleic acid may be from *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Enterobacter cloacae*, *Helicobacter pylori*, *Naisseria gonorrhoeae*, *Enterococcus faecalis*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Salmonella typhimurium*, *Saccharomyces cerevisiae*, *Candida albicans*, *Cryptococcus neoformans*, *Aspergillus fumigatus*, *Klebsiella pneumoniae*, *Salmonella typhi*, *Salmonella paratyphi*, *Salmonella cholerasuis*, *Staphylococcus epidermidis*, *Mycobacterium tuberculosis*, *Mycobacterium leprae*, *Treponema pallidum*, *bacillus anthracis*, *Yersinia pestis*, *Clostridium botulinum*, *Campylobacter jejuni or Chlamydia trachomatus*, *Chlamydia pneumoniae* or any species falling within the genera of any of the above species. The proliferation-required nucleic acids from an organism other than *E. coli* may be hybridized to the array under a variety of conditions which permit hybridization to occur when the probe has different levels of homology to the sequence on the microarray. This would provide an indication of homology across the organisms as well as clues to other possible essential genes in these organisms.

In still another embodiment, the exogenous nucleic acid sequences of the present invention that are identified as required for bacterial growth or proliferation can be used as antisense therapeutics for killing bacteria. The antisense sequences can be directed against the proliferation-required genes whose sequence corresponds to the exogenous nucleic acid probes identified here (i.e. the antisense nucleic acid may hybridize to the gene or a portion thereof). Alternatively, antisense therapeutics can be directed against operons in which proliferation-required genes reside (i.e. the antisense nucleic acid may hybridize to any gene in the operon in which the proliferation-required genes reside). Further, antisense

therapeutics can be directed against a profiferation-required gene or portion thereof with or without adjacent noncoding sequences, an intragenic sequence (i.e. a sequence between genes), a sequence spanning at least a portion of two or more genes, a 5' noncoding region or a 3' noncoding region located upstream or downstream from the actual sequence that is required for bacterial proliferation or an operon containing a proliferation-required gene.

In addition to therapeutic applications, the present invention encompasses the use of nucleic acid sequences complementary to sequences required for proliferation as diagnostic tools. For example, nucleic acid probes complementary to proliferation-required sequences that are specific for particular species of microorganisms can be used as probes to identify particular microorganism species in clinical specimens. This utility provides a rapid and dependable method by which to identify the causative agent or agents of a bacterial infection. This utility would provide clinicians the ability to prescribe species specific antimicrobial compounds to treat such infections. In an extension of this utility, antibodies generated against proteins translated from mRNA transcribed from proliferation-required sequences can also be used to screen for specific microorganisms that produce such proteins in a species-specific manner.

The following examples teach the genes of the present invention and a subset of uses for the *E. coli* genes identified as required for proliferation. These examples are illustrative only and are not intended to limit the scope of the present invention.

EXAMPLES

The following examples are directed to the identification and exploitation of *E. coli* genes required for proliferation. Methods of gene identification are discussed as well as a variety of methods to utilize the identified sequences.

Genes Identified as Required for Proliferation of E. coli

Exogenous nucleic acid sequences were cloned into an inducible expression vector and assayed for growth inhibition activity. Example 1 describes the examination of a library of exogenous nucleic acid sequences cloned into IPTG-inducible expression vectors. Upon activation or induction, the expression vectors produced an RNA molecule corresponding to the subcloned exogenous nucleic acid sequences. The RNA product was in an antisense orientation with respect to the *E. coli* genes from which it was originally derived. This antisense RNA then interacted with sense mRNA produced from various *E. coli* genes and interfered with or inhibited the translation of the sense messenger RNA (mRNA) thus preventing protein production from these sense mRNA molecules. In cases where the sense mRNA encoded a protein required for the proliferation, bacterial cells containing an activated expression vector failed to grow or grew at a substantially reduced rate,

EXAMPLE 1

Inhibition of Bacterial Proliferation after IPTG induction

To study the effects of transcriptional induction in liquid medium, growth curves were carried out by back diluting cultures 1:200 into fresh media with or without 1 mM IPTG and measuring the $0D_{450}$ every 30 minutes (min). To

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study the effects of transcriptional induction on solid medium, 10², 10³, 10⁴, 10⁵, 10⁶, 10⁷ and 10⁶ fold dilutions of overnight cultures were prepared. Aliquots of from 0.5 to 3 µl of these dilutions were spotted on selective agar plates with or without 1 mM IPTG. After overnight incubation, the plates were compared to assess the sensitivity of the clones to IPTG.

Of the numerous clones tested, some clones were identified as a containing sequence that inhibited *E. coli* growth after IPTG induction. Accordingly, the gene to which the inserted nucleic acid sequence corresponds, or a gene within the operon containing the inserted nucleic acid, may be required for proliferation in *E. coli*.

Characterization of Isolated Clones Negatively Affecting E. coll Proliferation

Following the identification of those expression vectors that, upon expression, negatively impacted *E. coli* growth or proliferation, the inserts or nucleic acid fragments contained in those expression vectors were isolated for subsequent characterization. Expression vectors of interest were subjected to nucleic acid sequence determination.

EXAMPLE 2

Nucleic Acid Sequence Determination of Identified Clones Expressing Nucleic Acid Fragments with Detrimental Effects of E.

coli Proliferation

The nucleotide sequences for the exogenous identified sequences were determined using plasmid DNA isolated using QIAPREP (Qiagen, Valencia, CA) and methods supplied by the manufacturer. The primers used for sequencing the inserts were 5' - TGTTTATCAGACCGCTT - 3' (SEQ ID NO: 403) and 5' - ACAATTTCACACAGCCTC - 3' (SEQ ID NO: 404). These sequences flank the polylinker in pLEX5BA. Sequence identification numbers (SEQ ID NOs) for the identified inserts are listed in Table I and discussed below.

EXAMPLE 3

Comparison Of Isolated Sequences to Known Sequences

The nucleic acid sequences of the subcloned fragments obtained from the expression vectors discussed above were compared to known *E. coli* sequences in GenBank using BLAST version 1.4 or version 2.0.8 using the following default parameters: Filtering off, cost to open a gap-5, cost to extend a gap-2, penalty for a mismatch in the blast portion of run-1, expectation value (e)-10.0, word size-11, number of one-line descriptions -100, number of alignments to show (B)-100. BLAST is described in Altschul, J Mol Biol. 215:403-10 (1990), the disclosure of which is incorporated herein by reference in its entirety. Expression vectors were found to contain nucleic acid sequences in both the sense and antisense orientations. The presence of known genes, open reading frames, and ribosome binding sites was determined by comparison to public databases holding genetic information and various computer programs such as the Genetics Computer Group programs FRAMES and CODONPREFERENCE. Clones were designated as "antisense" if the cloned fragment was oriented to the promoter such that the RNA trenscript produced was complementary to the expressed mRNA from a chromosomal locus. Clones were designated as "sense" if they coded for an RNA fragment that was identical to a portion of a wild type mRNA from a chromosomal locus.

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The sequences described in Examples 1-2 that inhibited bacterial proliferation and contained gene fregments in an antisense orientation are listed in Table I. This table lists each identified sequence by: a sequence identification number; a Molecule Number; a gane to which the identified sequence corresponds, listed according to the National Center for Biotechnology Information (NCBI), Blattner (Science 277:1453-1474(1997); also contains the *E. coli* K-12 genome sequence), or Rudd (Micro. and Mol. Rev. 62:985-1019 (1998)), (both papers are hereby incorporated by reference) nomenclatures. The CONTIG numbers for each identified sequence is shown, as well as the location of the first and last base pairs located on the *E. coli* chromosome. A Molecule Number with a **** indicates a clone corresponding to an intergenic sequence.

The sequences of the nucleic acid inserts of SEQ ID NOs: 1-81 from U.S. Provisional Patent Application No. 60/117,405 which inhibited proliferation were further analyzed. The reanalyzed sequences corresponding to SEQ ID NOs. 1-81 of U.S. Provisional Patent Application No. 60/117,405 have SEQ ID NOs. 405-485 in the present application.

SEQ ID NOs: 82-242 in U.S. Provisional Patent Application No. 60/117,405 are identical to SEQ ID NOs: 82-242 of the present application with the following exceptions. SEQ ID NO: 148 in the present application is the complementary strand of SEQ ID NO: 148 in U.S. Provisional Patent Application No. 60/117,405. Accordingly, the protein of SEQ ID NO: 308 which is encoded by SEQ ID NO: 148 has also been revised. SEQ ID NO: 163 in the present application is the complementary strand of SEQ ID NO: 163 in U.S. Provisional Patent Application No. 60/117,405. Accordingly, the protein of SEQ ID NO: 323 which is encoded by SEQ ID NO: 163 has also been revised.

The target gene of SEO ID NOs. 18 and 19 of U.S. Provisional Patent Application No. 60/117,405 (SEO ID NOs. 18, 19, 422, 423 of the present application) has been revised from dicF to ftsZ to reflect the fact that these SEO ID NOs. include natural antisense molecules which inhibit ftsZ expression.

The gene products of the nucleic acids of SEQ ID NOs. 198 and 239-242 in U.S. Provisional Patent Application No. 60/117,405 and in the present application (SEQ ID NOs. 358 and 399-402 of the present application) have been revised to reflect the fact that these nucleic acids encode nontranslated tRNAs and rRNAs. Tables I and II have been revised accordingly. The SEQ ID NOs. in Table II were also revised to reflect the fact that SEQ ID NOs. 89 and 402 were identical in U.S. Provisional Patent Application No. 60/117,405.

TABLE | Identified Clones with Corresponding Genes and Operons

SEQ ID NO.	Molecule No.	Gene (NCBI)	Gene (Blattner)	Gene (Rudd)	CONTIG
1, 405	EcXA001	yħħΩ	b3471	γhhQ	AE000423
2, 406	EcXA002	lep8	lepB	lepB	AE000343
3, 407	EcXA003	f586	b0955	ycbZ	AE000197
4, 408	EcXA004	rpsG, rpsL	b3341	rpsG, rpsL	AE000410
5, 409	EcXA005a	rplL, rplJ	b3986	rpIL, rpIJ	AE000472
6, 410	EcXA005b	rp/L	rp/L	rp/L	AE000472
7,411	EcXA005c	rplL, rplJ	rplL, rplJ	rpIL, rpIJ	AE000472
8, 412	EcXA005d	rplL, rpLJ	rp/L, rpU	rplL, rplJ	AE000472
9, 413	EcXA005a	rp/L	rpIL	rpIL	AE000472

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SEQ ID NO.	Molecule No.	Gene (NCBI)	Gene (Blattner)	Gene (Rudd)	CONTIG
10, 414	EcXA0051	rplL	rpiL		AE00047
11, 415	EcXA005g	rpiL			AE00047
12, 416	EcXA006	pta		+	AEDOD31
13, 417	EcXA007	yicP	*	+	AE00044
14, 418	EcXA008a	yhaU	b3127		AE000384
15, 419	EcXA008b	yhaU	yhati		AE000394
16, 420	EcXA008c	yhaU	yhaU		AE000394
17, 421	EcXA009	ydeY	ydeY		AE00034
18, 422	EcXA010a	dicF	61575		AE00025
	(natural as)		1		AC00023.
19, 423	EcXA010b	dicF	dicF	dicF	AE00025
20, 424	EcXA011	fdnG	61474		AE00024
21, 425	EcXA012a	fusA	b3340		AE00021
22, 426	EcXA012b	fusA	fusA	fusA	AE000410
23. 427	EcXA012c	fusA	fusA	fusA	AE000410
24, 428	EcXA013a	086	b2562	yfhL	AE000342
25, 429	EcXA013b	086	b2562	yfhL	AE000342
26, 430	EcXA013c	086	b2562	yfhL	AE000342
27, 431	EcXA014	visC	b2906	visC	AE000374
28, 432	EcXA015	yfdl	vfd/	yfdl	AE000374
29, 433	EcXA016	yeaQ	yeaQ	yeaQ	AE000323
		yoaG	yoaG	yoaG	AEUUUZ74
30, 434	EcXA017a	yggE	b2922		AE000375
31, 435	EcXA017b	yggE yggE	yggE	yggE E	
32, 436	EcXA018a	0464	b2074	yggE	AE000375
33, 437	EcXA018b	0464	b2074	yegM	AE000297
34, 438	EcXA019a	yehA	vehA	yegM	AE000297
71, 100	EUNAUTUU	yeren	уепя	yehA	AE000300
35, 439	EcXA019b	o172, yehA	o172, yehA	0172 wohl	AE000299
36, 440	EcXA020	0384, f82	61794, 61795	0172, yehA	AE000299
37, 441	EcXA021a	1112	b0218	yeaP, yeaQ	AE000274
8, 442	EcXA021b	1112		yafU	AE000130
39, 443	EcXA022	0740	b0218	yafU	AE000130
10, 444	EcXA023a	1176, 1382	b1629	ydgN	AE000258
1, 445	EcXA023b		b1504, b1505	ydeS, ydeT	AE000247
2, 446	EcXA0238	f176, f382 ygjM, ygjN	b1504, b1505	ydeS, ydeT	AE000247
3, 447	EcXA024		b3082	ygjM, ygjN	AE000390
4, 448		02383	b1878	yeeJ	AE000289
5, 449	EcXA026	061	Unpre-dicted	Unpre-dicted	AE000138
	EcXA027a	yohH	yohH	yohH	AE000303
6, 450 7, 451	EcXA027b	yohH	yohH	yohH	AE000303
7,431	EcXAD27c	yohH	yohH	yohH	AE000303
0.450	C-V40071	yoh!	yohi	yoh!	
8, 452	EcXA027d	yohH	yohH	yohH	AE000303
9, 453	EcXA028	f296	b2305	yfcl	AE000319
0, 454	EcXA029	yjjK	<u>64391</u>	ŊjK	AE000509
1,455	EcXA030	yi5A	b3557	yi5A	AE000433
2, 456	EcXA031	rplE	B3308	rplE	AE000408
3, 457	EcXA032a	ybgD	ybgD	ybg₽	AE000175
4, 458	EcXA032b**	ybgD	ybg⊅	ybgD	AE000175

-24-

gitA

1477

cspA

cspA

yhjU

ygjF

099

ydeH

sieB

ybbD

1234

rp/Y

ηĮΥ

ybgB

cydA

purB

CSTA

serV

yefE

yaiC

rp/W

infC

gor

rdG

196, csp8 196, csp8

fimE, fimA

o467, o222

rpl8, rplW

InsB 6

1477 (as)

Gene

(Blattner)

gltA

b3052

b3052

b3556

b3556

63101

b3100,

b1535

61353

63445

61138

rplY

rp[Y

ybgB

cydA

61131

CSTA

serv

yefE

rp/W

infC

gor

rplF

rdG

b0385

yaiU,yaiV

rplB, rplW

b4313

yhjU

Gene

(Rudd)

gltA

waaE

WBBE

cspA

yhjU

yqjF

yąjK

ydeH

sieB

vbbD

insB 6

vmfE

rplY

rpIY

ybg8

cydA

purB

csrA

serV

yelE,

<u>yaiC</u>

rp/W

infC

goi

rplF

rrlG

fimE, fimA

cspB, ydfS

yaiU, yaiV

rplB, rplW

CONTIG

AE000387 AE000386

AE000387

AE000433

AE000433

AE000431

AE000392

AE000251

AE000233

AE000156

AE000420

AE000214

AE000308

AE000308

AE000176

AE000213

AE000353

AE000502

AE000252

AE000294

AE000145

AE000144

AE000408

AE000408

AE000267 AE000266

AE000426

AE000408

AE000345

Gene

(NCBI)

SEQ ID

NO.

55, 459

56, 460

57, 461

58, 462

59, 463

60, 464

61, 465

62, 466

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66, 470

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68, 472

69, 473

70, 474

71, 475

72,478

73, 477

74, 478

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76, 480

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79,483

80, 484

81,485

Molecule No.

EcXA033a

EcXA033b

EcXA034a

EcXA034b

EcXA035

EcXA036

EcXA037

EcXA038

EcXA039

EcXA040

EcXA041

EcXA042a

EcXA042b

EcXA043

EcXA044

EcXA045**

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EXAMPLE 4

Identification of Genes and their Corresponding Operons Affected by Antisense Inhibition

The sequencing of the entire E. coli genome is described in Blattner et al., Science 277:1453-1474(1997) the entirety of which is hereby incorporated by reference and the sequence of the genome is listed in GenBank Accession No.U00096, the disclosure of which is incorporated herein by reference in its entirety. The operons to which the proliferation-inhibiting nucleic acids correspond were identified using RegulonDB and information in the Eterature. The coordinates of the boundaries of these operons on the E. coli genome are listed in Table III. Table III lists the molecule numbers of the inserts containing the growth inhibiting nucleic acid fragments, the genes in the operons corresponding to the inserts, the SEQ ID NOs of the genes containing the inserts, the SEQ ID NOs of the proteins encoded by the genes, the start and stop points of the genes on the E. coli genome, the orientation of the genes on the genome, whether the operons

are predicted or documented, and the predicted functions of the genes. The identified operons, their putative functions, and whether or not the genes are presently thought to be required for proliferation are discussed below.

Functions for the identified genes were determined by using either Blattner functional class designations or by comparing identified sequence with known sequences in various databases. A variety of biological functions were noted for the genes to which the clones of the present invention correspond. The functions for the genes of interest appear in Table II.

The proteins that are listed in Table II are involved in a wide range of biological functions.

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TABLE II
All Operon Data with Whole Chromosome Coordinates

Blattner functional class Predicted functional class of encoded proteins	Hypothetical outer membrane profein	Resistance to phage C1; periplasmic protein perhaps anchored to inner membrane	Secretion	Protease	Translation (Elongation factor Tu)	Transtation (elongation	Translation	Translation (rRNA)	Translation	Translation	Translation	Carbon compound	Probable adenine deaminase
Blattner functional class of encoded proteins	Hypothetical ORF, unclassified, unknown	Hypothetical ORF, unclassified, unknown	Transport and binding proteins	Unknown	Translation, post- translational modification	Carbon compound	Hypothetical ORF,						
Predicted (P) Or Documented (D) Operon	G.		(A)	(F)	ē					(0)		(a)	(P)
Right Coordinate	3607513	3608143	2703329	1017522	3468966	3471151	3471718	2729178	3471815	4178071	4178503	2414911	3843357
Left Coordinate	3606848	3607532	2702355	1015762	3467782	3469037	3471179	2727636	3471815	4177574	4178138	2412767	3841591
Genes On Operon	rhha	dcrB	8daj	ZqoA	tufA	fusA	рѕф	эги	rpsL	Πde	Ildu	ејб	yicP
Mole. No.	EcXA001		EcXA002	EcXA003	EcXA004			EcXA055		EcXA005a-9		EcXA006	EcXA007
Gena Prod. Seq ID No.	243	244	245	246	247	248	249	402	250	251	252	253	254
GeneSeq ID No.	82	83	84	85	98	87	88		8	91	92	93	\$

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Predicted functional clas					Probable integral membrane protein Phthalate permease	family		Putative ABC transporter							Regulator of cell division		Anaerobic respiration (formate debydro-nenase)				No homologues, no motifs	Ubiquinone synthesis
Blattner functional class Predicted functional class of encoded proteins		Hypothetical ORF,	Putative enzymes	Hypothetical ORF, unclassified, unknown	Carbon compound catabolism		Putative transport proteins	Putative transport proteins Putative ABC transporter	Hypothetical ORF,	unclassified, unknown	Hypothetical ORF, unclassified, unknown	Hypothetical ORF,	unclassified, unknown	Hypothetical ORF,	Cell processes (incl.	Adaptation, protection)	Energy metabolism	Energy metabolism	Energy metabolism		Hypothetical ORF, unclassified unknown	
Predicted (P) Or	Documented (D)	(a)					<u>r</u>								(a)	Ī	3				[d]	(d)
Right Coordinate		3269492	3270407	3271198	3272548	00000	1001049	1602071	1603063		1604097	1604999		1605313	106456	0070730	7/8860	1549369	1550015		2697943	3050337
Genes On Left Coordinate		3268266	3269508	3270428	3271214	1500514	1033014	1601043	1602071		1603075	1604124		1605023	105305	1545425	C7+C+C1	1548485	1549362		2697683	3049135
Genes On Operon		yhaD	Jey	yhaf	VhaU	λ ζ	Yuev	rdeY	yde.Z		упеА	Rauk		Jaw	<i>Z</i> 51 <i>J</i>	Chil	Dila	Hupj	tdnl	Same operon as EcXA004	yht	Jsin
Mole. No.		EcXA008a.c				Ervano	COUNTY								EcXA010a-b	FeX A 011	TOWAS .			EcXA 012a·c	EcXA013a-c	EcXA014
Gene Prod. Seq ID No.		255	256	257	258	250	3	260	261		797	763		264	265	388	3	267	268		269	270
GeneSeq 10	No.	95	88	97	88	g	3	200	<u>=</u>		701	50		104	.501	90.	3	107	8		109	110

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Blattner functional class Predicted functional class	of peroded proteins													Putative membrane protein		Homologies to transmis-	cosylase associated protein		No homologues				Homologues in multiple	oactena, no motifs	Transport (multiple	transferable resistance)						Weak homology to pilin
_				Biosynthesis of cofactors,	prosthetic groups and	carriers	Translation, post-	translational modification	Hypothetical ORF,	unclassified, unknown	Hypothetical ORF,	unclassified, unknown	Cell structure	Hypothetical ORF,	unclassified, unknown	Hypothetical ORF.	unclassified, unknown		Hypothetical ORF,	unclassified, unknown	Hypothetical ORF,		ou ucturar proteins		Futative fransport proteins Transport (multiple		Hypothetical ORF,	unclassified, unknown	Hypothetical ORF,	unclassified, unknown	Putative transport proteins	1
Predicted (P)	ō	Documented	Operon								Ð					(P)			€			ē			Ξ				=	3	4	(P)
Right	Coordinate			3051538			3052860		3053470		2466237		2467154	2468482		1877279			1877609		1877972	3058100		2152205	C07CE17		2156407		2159485		2160301	2186434
Left Coordinate				3050360			3051535		3052886		2465875		2466234	2467151		1877031			1877427		1877613	3065360		2151891	201214	2472207	C875C17	00.01.00	2156408	2010100	7123480	2185400
Genes On	Operon		/	Hiqn		,	ded		Ngt8		7105		YtdH	rtal		реэл		ļ	yoat	,	year	YouE	}	Noav		/Book	Misal	9	ngal	00000	ofia	yehA
Mole. No.		•								2,000	ECARUIS					EcxA016						EcXA017a-b		EcXA018a-b							. 0000	ECAAU19a-b
Gene Prod.	Sed to No.			271		27.0	7/7	27.0	37	97.0	+/7	326	6//3	5/2	1	//7		27.0	9/7	970	6/7	280		281		282		283		284	195	697
GeneSeq	e ;	e e		Ξ		112	!	113	2	-	:	116		<u> </u>	::	<u> </u>		=	2	110	<u> </u>	120		121		122	!	123	?	124	363	671

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Blattner functional class Predicted functional class	of encoded proteins								Homologues in H. Inf. and S.	Pombe., no motifs,	transmem-brane region	present																	fimf-like	
$\overline{}$	of encoded proteins		Hypothetical ORF,	Putative changennes	Cell etructure				Hypothetical ORF,	unclassified, unknown			Hypothetical ORF,	unclassified, unknown	Transcription, RNA	processing and degradation	Hynnthotical DRE	unclassified, unknown		unclassified, unknown										
Predicted (P)	ŏ	Documented (D) Operon							B				€														(d)			
Right	Coordinate		2188930	2189665	2190242				239084				1704372		1704950		1707165		1708224		1708848		1709547		1710182		1586320		1586863	
Left Coordinate			2186450	2188946	2189700				238746				1703791		1704372		1704943		1707166		1708228		1708852		1709547	_	1585817		1586333	
Genes On	Operon		8yaA	Jyak	Qyak	Same operon	as EcXA018	two)	yafU				rágí		Noby		Ngol		ngb/		AbpA		nggA		ath	-	удея		rdeS	1
Mole. No.						EcXA020			EcxA021a-b				EcXA022										~				EcXA023a-b		-	
Gene Prod.	Sed ID No.		286	287	288				289				230		167	100	767	1		100		200	667		967		297		298	
GeneSeq		HO.	126	127	128				129				25.		=		751	.::	3	76.	<u>\$</u>	136	2		9		137		138	1

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Blattner functional class Predicted functional class	of encoded aroteins		find-like	Weak homology to long	chain fatty acid coa ligase in	Archaeglobus	Homologues in various	bacteria	Strong similarity to	numerous attaching and	effacing proteins and	nifm fike		Xylose binding protein-like			Similar to S. Typhi histidine	transport gene	Similar to ABC transporter		IS150 orf A								
Blattner functional class	of encoded proteins		Structural proteins	Hypothetical ORF,	unclassified, unknown		Hypothetical ORF,	unclassified, unknown	Hypothetical ORF,	unclassified, unknown			Putative fransport proteins	Hypothetical ORF,	unclassified, unknown	Putative regulatory protein		DWI		unclassified, unknown		unclassified, unknown	Phage, transposon, or	plasmid	Translation, post-	translational modification	Putative transport proteins	Translation, post-	translational modification
Predicted (P)	ŏ	Documented (D)		((P)		-	unpredicted	(A)			€	Œ.		<u>B</u>		(F)		-		ē	_			-
Right	Coordinate		1588025	3231785			3232096		2020036			331184	2226539	2226859		2228405	2421559		4628091		3718830		3719678		3440371		3441734	3442176	
Left Coordinate			1586877	3231369			3231782		2042885			331001	2225343	2226569		2227458	2420669		4626424		3718309		3718627		3440255		3440403	3441742	
Genes On	Operon		ydeT	NgjM			VigiN		reeJ			Kier	Syote	Уир		Hoy	hc//		XIIX		ri5A		yi58		/wds		priA	OJds	
Mole. No.				EcXA024					EcXA025			EcXA026	EcXA027a-d				EcXA028		ECXAU29		EcXA030				ECXAU31				
Gene Prod.	Sed ID No.		299	96			<u></u>		302			303	304	 8		306	307	18	en En				310		=		312	313	
GeneSeq	2	No.	139	140			141		142			143	14	145		146	147		8		143		3		5		761	153	

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Blattner functional class Predicted functional class of encoded proteins					Translation				Translation				Hypothetical fimbrial protein		Glutamine biosynthesis	ADP heptose synthase/	autotrophic growth protein			Data -	niva ciidperonin	
Blattner functional class of encoded proteins		Translation, post-	Translation, post-	translational modification Translation, post	translational modification Translation, post-	translational modification Translation, post-	translational modification Translation nost.	translational modification	Translation, post- translational modification	Translation, post-	translational modification	Franslational modification	Cell processes (incl.	Adaptation, protection)	Energy metabolism	Putative enzymes	100	rranslation, post- translational modification	Hypothetical ORF,	Unclassified, unknown	(10)	Translation, post-
Predicted (P) Or	Documented (D)												æ		6	Ē				5		(d.)
Right Coordinate		3442359	3442866	3443234	3443777	3444182	3444521		3445075	3445404	2445700	00/0445	752018		753691	3194394	2107707	707/210	3198606	3717890		3695658
Genes On Left Coordinate Operon		3442180	3442363	3442881	3443244	3443790	3444216		3444536	3445090	2445415	24240	751452	000	/52408	3192961	3104447	7	3197305	3717678		3694087
Genes On Operon		Ошал	ıpsE	RIdu	plF	Hsqs	Nsqr	,	ald.	Xldı	Mar		Obak		ditt	waat	Juju		rgiř	cspA		Siful
MOJE. NG.													EcXA032a-b		7.0000	ECAAU338-D				EcXA034a-b		EcxA035
Seq 10 No.		314	315	316	317	318	319	000	350	321	322	!	323	800	324	275	326		327	328		329
Ol	Ko.	154	155	158	157	158	159	655	001	161	162	!	豆	2	3 5	<u> </u>	166		167	158		

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Blattner functional class Predicted functional class	of encoded proteins		Regions similar to dehydro- genases, nucleases etc.					Homologues in many bacteria, blocks; secretion/ ATP synthase/ftsz	Similar to carbony-kinase, oxidase, symporters	Super-infection exclusion factor B-like				Rhs-like element	ATP synthase, desaturase
Blattner functional class	of encoded proteins	Hypothetical ORF, unclassified, unknown	Hypothetical ORF, unclassified, unknown	Hypothetical ORF, unclassified, unknown	Hypothetical ORF, unclassified, unknown	Hypothetical ORF, unclassified, unknown	Similar to mukb from H. Inf.	Hypothetical ORF, unclassifted, unknown	Hypothetical ORF, unclassified, unknown	Phage, transposon, or plasmid	Hypothetical ORF, unclassified, unknown	Hypothatical ORF, unclassified, unknown	Hypothetical ORF, unclassified, unknown		
Predicted (P)	Or Documented (D) Operon			(P)				(d)	(P)	(P)		<u>a</u>			
Right	Coordinate	3695846	3697522	3246977	3247320	3247727	3248016	3248594	1621874	1417183	1417368	526765	527173	527883	528124
Genes On Left Coordinate		3695658	3695843	3246594	3247015	3247323	3247717	3248112	1620984	1416572	1417192	522485	526805	527173	527864
Genes On	Operon	rhjT	niyA .	yajC	ОфА	yąĘ	yajK	YąjF	Нар	sieB	rajB (b1354)	Ostu	уррС	HqlA	Ogqx
Mole. No.				EcXA036					EcXA037	EcXA038		EcXA039			
Gene Prod.	Seq ID No.	330	331	332	333	334	335	336	337	338	339	340	341	342	343
GeneSeq	Z Z	071	171	172	173	174	175	176	177	178	179	180	181	182	183

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Blattner functional class Predicted functional class	of encoded proteins									No assigned role		No assigned role		Translation				Unknown		Cytochrome D oxidase		Purine biosynthesis		Carbon storage regulator	(mRNA decay factor)	Translation (tRNA)			Fimbrae	Requiator of inversion
Blattner functional class	of encoded proteins	Hypothetical ORF,	Phage, transposon, or	plasmid	Phage, transposon, or plasmid	Hypothetical ORF,	unclassified, unknown	Hypothetical ORF,	unclassified, unknown	Hypothetical ORF,	UIICASSIIBO, UAKIOWA	Hypothetical ORF,	unclassified, unknown	Translation, post-	translational modification	Translation, post-	translational modification	Carbon compound	catabolism	Energy metabolism	Energy metabolism	Nucleotide biosynthesis and Purine biosynthesis	metabolism	Regulatory function		Translation, post-	fication	Cell structure		Cell structure
Predicted (P)	Occumented (D)		(P)							€				(P)		Ð				ê		(D)		<u>a</u>		Unpredicted		(0)		
Right		528354	351389		3581811	3581085		3580672		1196755		1197460		2280821		767183		769834		772249	773404	1191209		2817168		2816667		4539127	4540201	4541231
Left Coordinate		528163	351114		351308	3580669		3579494		1196090		1196756		2280537		765207		767201		770678	772265	1189839		2816983		2816575		4538525	4539605	4540683
Genes On		ĮQIÁ	insB_6		insA	yrthA	•	ythZ		OJW.		ymit		Дď		hzA		86¢/		cydA	cydB	bur8		csrA		_res		limB	fimE	fimA
Mole. No.			EcXA040							EcXA041				EcXA042a-b		EcXA043						EcxA044		EcXA045				EcXA046		
Gene Prod.		344	345		346	347		348		28	200	320		321		352		353		354	355	356		357		358		359	360	361
GeneSeq		18	185		186	187		188		189		3		161		192		5		20	195	85		197		198		199	200	201

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Predicted functional cl	of encoded prateins														Lysis protein												UDP galacto-pyranase	mutase	Unknown		Putativa auto-transporter
Blattner functional class Predicted functional class	of encoded proteins		Celi structure	Cell structure	Cell structure	Cell etructure	Cell etricting	Cell stricture	Hypothetical ORF,	unclassified, unknown	Hypothetical ORF,	unclassified, unknown	Hypothetical ORF,	unclassified, unknown		W.	Cell processes (incl.	Adaptation, protection)	Phage, transposon, or	plasmid	Putative enzymes	Hypothetical ORF,	Pirtative enginee	Hypothetical ORF,	unclassified, unknown	Cell structure		unclassified, unknown		unclassified, unknown	Putative enzymes P.
Predicted (P)	Or Documented (D)	Operan							Œ								<u> </u>		Ē.							0		Đ	(a)		<u>a </u>
Right	Coordinate		4541835	4542597	4545301	4545841	4546357	4547279	1638684		1638081		1638389		1638684		1639578		2100933		2101411	2102531	2103106	2104079		2105248	2106351		404042		393642
Genes On Left Coordinate			4541188	4541872	4542665	4545311	4545854	4546377	1637054		1637548		1638078		1638394		1639363		2099917	0100010	2100938	2101413	2102516	2103087		2104082	2105248		402927		392239
Genes On	Operon		timl	TimC	Qwij	fimF	Smit	Huij	dipA		rata		ydfR		Sypi		gdso		Vi52_7		ria/	Jel	HJak	Эјэл		υlc	refE		raiC		yaıÜ
Mole. No.									EcXA047				٠						ECXAU48										ECXA049	0.000	ECAAUSU
Sea In No			362	363	364	365	366	367	368	-	999	1	3/0		Ş	27.0	3/5		5/5	374	1	3/5	376	377	-	3/8	379) R	200	300
GeneSeq	<u> </u>		202	203	204	202	206	207	208	000	507		710		117	25.5	717	212	 612	214	1	617	216	217		617	218	000	 37	100	77

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Predicted functional clas	of encoded proteins				Hypothatical outer	membrane protein			ſ										Translation		Translation												Translation	
Predicted (P) Blattner functional class Predicted functional class	of encoded proteins				Hypothetical ORF,	unclassified, unknown	Translation, post-	translational modification	Translation, post-	transfational modification	Translation, post-	translational modification	Franslation, post-	translational modification	Translation, post-	translational modification	Translation, post-	translational modification	Translation, post-	translational modification		translational modification												
Predicted (P)	ŏ	Documented	ê	Operon			6																				•		ē					_
Right	Coordinate				394353		3446205		3446396		3446806		3447520		3447870		3448163		3449001		3449321		3449923		3450563		3450907		1797773		1798023		1798662	
Genes On Left Coordinate					393685		3445951		3446205		3446396		3446819		3447538		3447885		3448180		3449019		3449318		3449934		3450596		1797417		1797826		1798120	
Genes On	Operon				Viev		Dsds		Judi		djds		Jsdı		Ndı		Ssdi		8Jds		Wids		ajds		Jdu		/sdi		IJdı		lmd1		julC	
Male. No.							EcXA051a-b																						EcXA052					
Gene Prod.	Seq ID No.				382		383		384		385		986		387		388		389		330		 		382		383		ž Ž		382		386	
GeneSeq	2	ž			727		223		224		225		528		227		228		528		230		53		737		733		73. 73. 73.		532		88	

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Predicted functional class of encoded proteins			Glutathione oxido-reductase	ļ.		Translation (rRNA)		Translation (rRNA)		Translation (tRNA)		Translation (rRNA)	
Predicted (P) Blattner functional class Predicted functional class Or of encoded proteins of encoded proteins		Translation, post-	1	prosthetic groups and		1	translational modification		transfational modification	Г	translational modification	Translation, post-	translational modification
Predicted (P) Or Documented	(D) Operon		(P)			ê							
Right Coordinate		1800594	3645281			2727204		2724208		2727464		2729178	
Genes On Left Coordinate Operon		1798666	3643929	- 17- 1		2724301		2724089		2727389		2727636	
Genes Da Operon		thrS	sos		Same operon as EcXA031	gju		9,11		gltW		gsu	
Male. No.			EcXA053		EcXA054	EcXA055		٠					
GeneSeq Gene Prod. ID Seq ID No. No.		397	398			399		400		- -		402	
GeneSeq ID No.		237	238			239		740		241		242	

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Several of the expression vectors contain fragments that correspond to genes of unknown function or if the function is known, it is not known whether the gene is essential. For example, EcxA001, 003, 007, 008, 013, 015, 016, 017, 018, 019, 020, 021, 022, 023, 024, 025, 026, 027, 028, 029, 030, 032, 033, 034, 035, 036, 037, 038, 039, 040, 041, 047, 048, 049 and 050 are all exogenous nucleic acid sequences that correspond to *E. coli* proteins that have no known function or where the function has not been shown to be essential or nonessential.

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The present invention reports a number of novel *E. coli* genes and operans that are required for proliferation. From the list clone sequences identified here, each was identified to be a portion of a gene in an operan required for the proliferation of *E. coli*. Cloned sequences corresponding to genes already known to be required for proliferation in *E. coli* include EcXA002, 004, 005, 010, 012, 014, 031, 02, 043, 045, 051, 052, 054, and 055. The remaining identified sequences correspond to *E. coli* genes previously undesignated as required for proliferation in the art.

An interesting observation of the present invention is that there are also several sequence fragments that correspond to *E. coli* genes that are not thought to be required for *E. coli* proliferation. Nevertheless, under the conditions described above, the antisense expression of these gene fragments causes a reduction in cell growth. This result implies that the genes corresponding to the identified sequences are actually required for proliferation. Molecule Nos. corresponding to these genes are EcXAOO6, 044, 046, and 053.

Following identification of the sequences of interest, these sequences were localized into operons. Since bacterial genes are expressed in a polycistronic manner, the antisense inhibition of a single gene in an operon might effect the expression of all the other genes on the operon or the genes down stream from the single gene identified. In order to determine which of the gene products in an operon are required for proliferation, each of the genes contained within an operon may be analyzed for their effect on viability as described below.

TABLE III Operon Boundaries

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Uperon Boundaries											
Mole. No.	Left	Right									
	Coordinate	Coordinate									
EcXA001	3606848	360814									
EcXA002	2702355	2703329									
EcXA003	1015762	101752									
EcXA004	3467782	3472189									
EcXA005	4177574	4178503									
EcXA006	2412767	2414911									
EcXA007	3841591	3843357									
EcXA008	3268266	3272548									
EcXA009	1599514	1605313									
EcXA010	1647406	1647458									
EcXA011	1545425	1550015									
EcXA012	3467782	3472189									
EcXA013	2697683	2697943									
EcXA014	3049135	3053470									
EcXA015	2465875	2468482									
EcXA016	1877031	. 1877972									
EcXA017	3065360	3066100									
EcXA018	2151891	2160901									
EcXAD19	2185400	2190242									
EcXAD20	1877031	1877972									
EcXA021	238746	239084									
EcXA022	1703791	1710182									
EcXA023	1585817	1588025									
EcXA024	3231369	3232096									
EcXA025	2042885	2050036									
EcXA026	331001	331184									
EcXAD27c	2225343	2228405									
EcXA028	2420669	2421559									
EcXA029	4626424	4628091									
EcXA030	3718309	3719678									
EcXA031	3440255	3445786									
EcXA032b	751452	753691									
EcXA033	3192961	3198606									
EcXA034	3717678	3717890									
EcXA035	3694087	3697522									
EcXA036	3246594	3248594									
EcXA037	1620984	1621874									
EcXAD38	1416572	1417368									
EcXA039	522485	528354									
EcXA040	3580669	3580672									
EcXA041	1196090	1197460									
EcXA042	2280537	2280821									

Mole. No.	Left	Right
	Coordinate	Coordinate
EcXA043	765207	773404
EcXA044	1189839	1191209
EcXA045	2816575	2817168
EcXAD46	4538525	4547279
EcXA047	1637054	1639578
EcXA048	2099917	2106351
EcXA049	402927	404042
EcXA050	392239	394353
EcXA051	3445951	3450907
EcXA052	1797417	1800594
EcXA053	3643929	3645281
EcXA054	3440255	3445786
EcXA055	2724301	2729178

EXAMPLE 5

Identification of Individual Genes within an Operon Required for Proliferation

The following example illustrates a method for determining which gene in an operon is required for proliferation. The clone insert corresponding to Molecule No. EcXA004 possesses nucleic acid sequence homology to the *E. coli* genes rspG and rspL. This molecule corresponds to an operon containing two additional genes fusA and tufA. The rpsL gene is the first gene in the operon. To determine which gene or genes in this operon are required for proliferation, each gene is selectively inactivated using homologous recombination. Gene rpsL is the first gene to be inactivated.

Deletion inactivation of a chromosomal copy of a gene in *E. coli* can be accomplished by integrative gene replacement. The principle of this method (Hamilton, C. M., et al 1989. *J. Bacteriol.* 171: 4617-4622) is to construct a mutant allele of the targeted gene, introduce that ailele into the chromosome using a conditional suicide vector, and then force the removal of the native wild type allele and vector sequences. This will replace the native gene with a desired mutation(s) but leave promoters, operators, etc. intact. Essentiality of a gene is determined either by deduction from genetic analysis or by conditional expression of a wild type copy of the targeted gene (trans complementation).

The first step is to generate a mutant <code>rpsl</code> allele using PCR amplification. Two sets of PCR primers are chosen to produce a copy of <code>rpsl</code> with a large central deletion to inactivate the gene. In order to eliminate polar effects, it is desirable to construct a mutant allele comprising an in-frame deletion of most or all of the coding region of the <code>rpsl</code> gene. Each set of PCR primers is chosen such that, a region flanking the gene to be amplified is sufficiently long to allow recombination (typically at least 500 nucleotides on each side of the deletion). The targeted deletion or mutation will be contained within this fragment. To facilitate cloning of the PCR product, the PCR primers may also contain restriction endonuclease sites found in the cloning region of a conditional knockout vector such as pKO3 (Link, et al 1997 J. Bacteriol. 179 (20): 6228-6237). Suitable sites include Notl, Sall, BamHl and Smal. The <code>rpsl</code> gene fragments are produced using standard PCR conditions including, but not limited to, those outlined in the manufacturers directions for the

Hot Start Taq PCR kit (Qiagen, Inc., Valencia, CA). The PCR reactions will produce two fragments that can be fused together. Alternatively, crossover PCR can be used to generate a desired deletion in one step (Ho, S. N., et al 1989. *Gene* 77: 51-59, Horton, R. M., et al 1989. *Gene* 77: 61-68). The mutant allele thus produced is called a "null" allele because it cannot produce a functional gene product.

The mutant allele obtained from PCR amplification is cloned into the multiple cloning site of pKO3. Directional cloning of the *rpsl* null allele is not necessary. The pKO3 vector has a temperature-sensitive origin of replication derived from pSC101. Therefore, clones are propagated at the permissive temperature of 30°C. The vector also contains two selectable marker genes: one that confers resistance to chloramphenicol and another, the *Bacillus subtilis sacB* gene, that allows for counter-selection on sucrose containing growth medium. Clones that contain vector DNA with the null allele inserted are confirmed by restriction endonuclease analysis and DNA sequence analysis of isolated plasmid DNA. The plasmid containing the *rpsl* null allele insert is known as a knockout plasmid.

Once the knockout plasmid has been constructed and its sequence verified, it is transformed into a Rec* E. coli host cell. Transformation can be by any standard method such as electroporation. In some fraction of the transformed cells, plasmids will integrate into the E. coli chromosome by homologous recombination between the rpst null allele in the plasmid and the rpst gene in the chromosome. Transformant colonies in which such an event has occurred are readily selected by growth at the non-permissive temperature of 43°C and in the presence of choramphenicol. At this temperature, the plasmid will not replicate as an episome and will be lost from cells as they grow and divide. These cells are no longer resistant to chloramphenicol and will not grow when it is present. However, cells in which the knockout plasmid has integrated into the E. coli chromosome remain resistant to chloramphenicol and propagate.

Cells containing integrated knock-out plasmids are usually the result of a single crossover event that creates a tandem repeat of the mutant and native wild type alleles of *rpsL* separated by the vector sequences. A consequence of this is that *rpsL* will still be expressed in these cells. In order to determine if the gene is essential for growth, the wild type copy must be removed. This is accomplished by selecting for plasmid excision, a process in which homologous recombination between the two alleles results in looping out of the plasmid sequences. Cells that have undergone such an excision event and have lost plasmid sequences including *sacB* gene are selected for by addition of sucrose to the medium. The sacB gene product converts sucrose to a toxic molecule. Thus counter selection with sucrose ensures that plasmid sequences are no longer present in the cell. Loss of plasmid sequences is further confirmed by testing for sensitivity to chloramphenicol (loss of the chloramphenicol resistance gene). The latter test is important because occasionally a mutation in the *sacB* gene can occur resulting in a loss of *sacB* function with no effect on plasmid replication (Link, et. al., 1997 *J. Bacteriol.* 179 (20): 6228-6237). These artifact clones retain plasmid sequences and are therefore still resistant to chloramphenicol.

In the process of plasmid excision, one of the two rpsL alleles is lost from the chromosome along with the plasmid DNA. In general, it is equally likely that the null allele or the wild type allele will be lost. Therefore, if the rpsL

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gene is not essential, half of the clones obtained in this experiment will have the wild type allels on the chromosome and half will have the null allels. However, if the *rpsL* gene is essential, cells containing the null allels will not be obtained as a single copy of the null allels would be lethal.

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To determine the essentiality of *rpsl*, a statistically significant number of the resulting clones, at least 20, are analyzed by PCR amplification of the *rpsl* gene. Since the null allele is missing a significant portion of the *rpsl* gene, its PCR product is significantly shorter than that of the wild type gene and the two are readily distinguished by gel electrophoretic analysis. The PCR products may also be subjected to sequence determination for further confirmation by methods well known to those in the art.

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The above experiment is generally adequate for determining the essentiality of a gene such as rpsl. However, it may be necessary or desirable to more directly confirm the essentiality of the gene. There are several methods by which this can be accomplished. In general, these involve three steps: 1) construction of an episome containing a wild type allele, 2) isolation of clones containing a single chromosomal copy of the mutant null allele as described above but in the presence of the episomal wild type allele, and then 3) determining if the cells survive when the expression of the episomal allele is shut off. In this case, the trans copy of wild type rpsL is made by PCR cloning of the entire coding region of rpsL and inserting it in the sense orientation downstream of an inducible promoter such as the E. coli lac promoter. Transcription of this allele of rps1 will be induced in the presence of IPTG which inactivates the lac repressor. Under IPTG induction rpsL protein will be expressed as long as the recombinant gene also possesses a ribosomal binding site, also known as a "Shine-Dalgarno Sequence". The trans copy of rpst is cloned on a plasmid that is compatible with pSC101. Compatible vectors include p15A, pBR322, and the pUC plasmids, among others. Replication of the compatible plasmid will not be temperature-sensitive. The entire process of integrating the null allele of rpsL and subsequent plasmid excision is carried out in the presence of IPTG to ensure the expression of functional rpsL protein is maintained throughout. After the null rpsL allele is confirmed as integrated on the chromosome in place of the wild type rpsL allele, then IPTG is withdrawn and expression of functional rpsL protein shut off. If the rpsL gene is essential, cells will cease to proliferate under these conditions. However, if the rpsl gene is not essential, cells will continue to proliferate under these conditions. In this experiment, essentiality is determined by conditional expression of a wild type copy of the generather than inability to obtain the intended chromosomal disruption.

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30 *45* An advantage of this method over some other gene disruption techniques is that the targeted gene can be deleted or mutated without the introduction of large segments of foreign DNA. Therefore, polar effects on downstream genes are eliminated or minimized. There are methods described to introduce inducible promoters upstream of potential essential bacterial genes. However in such cases, polarity from multiple transcription start points can be a problem. One way of preventing this is to insert a gene disruption cassette that contains strong transcriptional terminators upstream of the integrated inducible promoter (Zhang, Y, and Cronan, J. E. 1996 J. Bacteriol. 178 (12): 3614-3620). The described techniques will all be familiar to one of ordinary skill in the art.

Following the analysis of the *rpsL* gene, the other genes of the operon are investigated to determine if they are required for proliferation.

EXAMPLE 6

Expression of the Proteins Encoded by Genes Identified as Required for E. coli Proliferation

The following is provided as one exemplary method to express the proliferation-required proteins encoded by the identified sequences described above. First, the initiation and termination codons for the gene are identified. If desired, methods for improving translation or expression of the protein are well known in the art. For example, if the nucleic acid encoding the polypeptide to be expressed lacks a methionine codon to serve as the initiation site, a strong Shine-Delgamo sequence, or a stop codon, these sequences can be added. Similarly, if the identified nucleic acid sequence lacks a transcription termination signal, this sequence can be added to the construct by, for example, splicing out such a sequence from an appropriate donor sequence. In addition, the coding sequence may be operably linked to a strong promoter or an inducible promoter if desired. The identified nucleic acid sequence or portion thereof encoding the polypeptide to be expressed is obtained by PCR from the bacterial expression vector or genome using oligonucleotide primers complementary to the identified nucleic acid sequence or portion thereof and containing restriction endonuclease sequences for Ncol incorporated into the 5' primer and 8gAl at the 5' end of the corresponding 3'-primer, taking care to ensure that the identified nucleic acid sequence is positioned in frame with the termination signal. The purified fragment obtained from the resulting PCR reaction is digested with Ncol and BgAl, purified and ligated to an expression vector.

The ligated product is transformed into DH5 α or some other *E. coli* strain suitable for the over expression of potential proteins. Transformation protocols are well known in the art. For example, transformation protocols are described in: Current Protocols in Molecular Biology, Vol. 1, Unit 1.8, (Ausubel, et al., Eds.) John Wiley & Sons, Inc. (1997). Positive transformants are selected after growing the transformed cells on plates containing 50-100 µg/ml Ampicillin (Sigma, St. Louis, Missouri). In one embodiment, the expressed protein is held in the cytoplasm of the host organism. In an alternate embodiment, the expressed protein is released into the culture medium. In still another alternative, the expressed protein can be sequestered in the periplasmic space and liberated therefrom using any one of a number of cell lysis techniques known in the art. For example, the osmotic shock cell lysis method described in Chapter 16 of Current Protocols in Molecular Biology, Vol. 2, (Ausubel, et al., Eds.) John Wiley & Sons, Inc. (1997). Each of these procedures can be used to express a proliferation-required protein.

Expressed proteins, whether in the culture medium or liberated from the periplasmic space or the cytoplasm, are then purified or enriched from the supernatant using conventional techniques such as ammonium sulfate precipitation, standard chromatography, immunoprecipitation, immunochromatography, size exclusion chromatography, ion exchange chromatography, and HPLC. Alternatively, the secreted protein can be in a sufficiently enriched or pure state in the supernatant or growth media of the host to permit it to be used for its intended purpose without further enrichment. The purity of the protein product

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obtained can be assessed using techniques such as Coomassie or silver staining or using antibodies against the control protein.

Coomassie and silver staining techniques are familiar to those skilled in the art.

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Antibodies capable of specifically recognizing the protein of interest can be generated using synthetic peptides using methods well known in the art. See, Antibodies: A Laboratory Manual, (Harlow and Lane, Eds.) Cold Spring Harbor Laboratory (1988). For example, 15-mer peptides having a sequence encoded by the appropriate identified gene sequence of interest or portion thereof can be chemically synthesized. The synthetic peptides are injected into mice to generate antibodies to the polypeptide encoded by the identified nucleic acid sequence of interest or portion thereof. Alternatively, samples of the protein expressed from the expression vectors discussed above can be purified and subjected to amino acid sequencing analysis to confirm the identity of the recombinantly expressed protein and subsequently used to raise antibodies. An Example describing in detail the generation of monoclonal and polyclonal antibodies appears in Example 7.

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The protein encoded by the identified nucleic acid sequence of interest or portion thereof can be purified using standard immunochromatography techniques. In such procedures, a solution containing the secreted protein, such as the culture medium or a cell extract, is applied to a column having antibodies against the secreted protein attached to the chromatography matrix. The secreted protein is allowed to bind the immunochromatography column. Thereafter, the column is washed to remove non-specifically bound proteins. The specifically bound secreted protein is then released from the column and recovered using standard techniques. These procedures are well known in the art.

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In an alternative protein purification scheme, the identified nucleic acid sequence of interest or portion thereof can be incorporated into expression vectors designed for use in purification schemes employing chimeric polypeptides. In such strategies the coding sequence of the identified nucleic acid sequence of interest or portion thereof is inserted in-frame with the gene encoding the other half of the chimera. The other half of the chimera can be maltose binding protein (MBP) or a nickel binding polypeptide encoding sequence. A chromatography matrix having antibody to MBP or nickel attached thereto is then used to purify the chimeric protein. Protease cleavage sites can be engineered between the MBP gene or the nickel binding polypeptide and the identified expected gene of interest, or portion thereof. Thus, the two polypeptides of the chimera can be separated from one another by protease digestion.

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One useful expression vector for generating maltose binding protein fusion proteins is pMAL (New England Biolabs), which encodes the malE gene. In the pMal protein fusion system, the cloned gene is inserted into a pMal vector downstream from the malE gene. This results in the expression of an M8P-fusion protein. The fusion protein is purified by affinity

EXAMPLE 7

chromatography. These techniques as described are well known to those skilled in the art of molecular biology.

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Production of an Antibody to an isolated E. coli Protein

Substantially pure protein or polypeptide is isolated from the transformed cells as described in Example 6. The concentration of protein in the final preparation is adjusted, for example, by concentration on a 10,000 molecular weight cut off

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AMICON filter device (Millipore, Bedford, MA), to the level of a few micrograms/ml. Monoclonal or polyclonal antibody to the protein can then be prepared as follows:

Monoclonal Antibody Production by Hybridoma Fusion

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Monoclonal antibody to epitopes of any of the peptides identified and isolated as described can be prepared from murine hybridomas according to the classical method of Kohler, G. and Müstein, C., Nature 256:495 (1975) or any of the well-known derivative methods thereof. Briefly, a mouse is repetitively inoculated with a few micrograms of the selected protein or peptides derived therefrom over a period of a few weeks. The mouse is then sacrificed, and the antibody producing cells of the spleen isolated. The spleen cells are fused by means of polyethylene glycol with mouse myeloma cells, and the excess unfused cells destroyed by growth of the system on selective media comprising aminopterin (HAT media). The successfully fused cells are diluted and aliquots of the dilution placed in wells of a microtiter plate where growth of the culture is continued. Antibody-producing clones are identified by detection of antibody in the supernatant fluid of the wells by immunoassay procedures, such as ELISA, as described by Engvall, E., "Enzyme immunoassay ELISA and EMIT," Meth. Enzymol. 70:419 (1980), and derivative methods thereof. Selected positive clones can be expanded and their monoclonal antibody product harvested for use. Detailed procedures for monoclonal antibody production are described in Davis, L. et al. Basic Methods in Molecular Biology Elsevier, New York. Section 21:2.

Polyclonal Antibody Production by Immunization

Polyclonal antiserum containing antibodies to heterogeneous epitopes of a single protein or a peptide can be prepared by immunizing suitable animals with the expressed protein or peptides derived therefrom described above, which can be unmodified or modified to enhance immunogenicity. Effective polyclonal antibody production is affected by many factors related both to the antigen and the host species. For example, small molecules tend to be less immunogenic than larger molecules and can require the use of carriers and adjuvant. Also, host animals vary in response to site of inoculations and dose, with both inadequate or excessive doses of antigen resulting in low titer antisera. Small doses (ng level) of antigen administered at multiple intradermal sites appears to be most reliable. An effective immunization protocol for rabbits can be found in Vaitukaitis, J. et al. J. Clin. Endocrinol. Metab. 33:988-991 (1971).

Booster injections can be given at regular intervals, and antiserum harvested when antibody titer thereof, as determined semi-quantitatively, for example, by double immunodiffusion in agar against known concentrations of the antigen, begins to fall. See, for example, Ouchterlany, O. et al., Chap. 19 in: Handbook of Experimental Immunology D. Wier (ed) Blackwell (1973). Plateau concentration of antibody is usually in the range of 0.1 to 0.2 mg/ml of serum (about 12 M). Affinity of the antisera for the antigen is determined by preparing compatitive binding curves, as described, for example, by Fisher, D., Chap. 42 in: Manual of Clinical Immunology, 2d Ed. (Rose and Friedman, Eds.) Amer. Soc. For Microbiol., Washington, D.C. (1980).

Antibody preparations prepared according to either protocol are useful in quantitative immunoassays which determine concentrations of antigen-bearing substances in biological samples; they are also used semi-quantitatively or qualitatively to

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identify the presence of antigen in a biological sample. The antibodies can also be used in therapeutic compositions for killing bacterial cells expressing the protein.

EXAMPLE 8

Screening Chemical Libraries

10 5 A. Protein-Based Assays

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Having isolated and expressed bacterial proteins shown to be required for bacterial proliferation, the present invention further contemplates the use of these expressed proteins in assays to screen libraries of compounds for potential drug candidates. The generation of chemical libraries is well known in the art. For example combinatorial chemistry can be used to generate a library of compounds to be screened in the assays described herein. A combinatorial chemical library is a collection of diverse chemical compounds generated by either chemical synthesis or biological synthesis by combining a number of chemical "building blocks" reagents. For example, a linear combinatorial chemical library such as a polypeptide library is formed by combining amino acids in every possible combination to yield peptides of a given length. Millions of chemical compounds theoretically can be synthesized through such combinatorial mixings of chemical building blocks. For example, one commentator observed that the systematic, combinatorial mixing of 100 interchangeable chemical building blocks results in the theoretical synthesis of 100 million tetrameric compounds or 10 billion pentameric compounds. (Gallop et al., "Applications of Combinatorial Technologies to Drug Discovery, Background and Peptide Combinatorial Libraries," Journal of Medicinal Chemistry, Vol. 37, No. 9, 1233-1250 (1994). Other chemical libraries known to those in the art may also be used, Including natural product libraries.

Once generated, combinatorial libraries can be screened for compounds that possess desirable biological properties. For example, compounds which may be useful as drugs or to develop drugs would likely have the ability to bind to the target protein identified, expressed and purified as discussed above. Further, if the identified target protein is an enzyme, candidate compounds would likely interfere with the enzymatic properties of the target protein. Any enzyme can be a target protein. For example, the enzymatic function of a target protein can be to serve as a protease, nuclease, phosphatase, dehydrogenase, transporter protein, transcriptional enzyme, and any other type of enzyme known or unknown. Thus, the present invention contemplates using the protein products described above to screen combinatorial chemical libraries.

Those in the art will appreciate that a number of techniques exist for characterizing target proteins in order to identify molecules useful for the discovery and development of therapeutics. For example, some techniques involve the generation and use of small peptides to probe and analyze target proteins both biochemically and genetically in order to identify and develop drug leads. Such techniques include the methods described in PCT publications No. W09935494, W09819162, W09954728, the disclosures of which are incorporated herein by reference in their entireties.

In another example, the target protein is a serine protease and the substrate of the enzyme is known. The present example is directed towards the analysis of libraries of compounds to identify compounds that function as inhibitors of the target enzyme. First, a library of small molecules is generated using methods of combinatorial library formation well known in

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the art. U.S. Patent NOs. 5,463,564 and 5,574, 656, to Agrafictis, et al., entitled "System and Method of Automatically Generating Chemical Compound with Desired Properties," are two such teachings. Then the library compounds are screened to identify library compounds that possess desired structural and functional properties. U.S. Patent No. 5,684,711 also discusses a method for screening libraries.

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To illustrate the screening process, the combined target and chemical compounds of the library are exposed to and permitted to interact with the purified enzyme. A labeled substrate is added to the incubation. The label on the substrate is such that a detectable signal is emitted from metabolized substrate molecules. The emission of this signal permits one to measure the effect of the combinatorial library compounds on the enzymatic activity of target enzymes. The characteristics of each library compound is encoded so that compounds demonstrating activity against the enzyme can be analyzed and features common to the various compounds identified can be isolated and combined into future iterations of libraries.

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Once a library of compounds is screened, subsequent libraries are generated using those chemical building blocks that possess the features shown in the first round of screen to have activity against the target enzyme. Using this method, subsequent iterations of candidate compounds will possess more and more of those structural and functional features required to inhibit the function of the target enzyme, until a group of enzyme inhibitors with high specificity for the enzyme can be found. These compounds can then be further tested for their safety and efficacy as antibiotics for use in mammals.

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It will be readily appreciated that this particular screening methodology is exemplary only. Other methods are well known to those skilled in the art. For example, a wide variety of screening techniques are known for a large number of naturally occurring targets when the biochemical function of the target protein is known.

B. Cell Based Assays

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Current cell-based assays used to identify or to characterize compounds for drug discovery and development frequently depend on detecting the ability of a test compound to inhibit the activity of a target molecule located within a cell or located on the surface of a cell. Most often such target molecules are proteins such as enzymes, receptors and the like. However, target molecules may also include other molecules such as DNAs, lipids, carbohydrates and RNAs including messenger RNAs, ribosomal RNAs, tRNAs and the like. A number of highly sensitive cell-based assay methods are available to those of skill in the art to detect binding and interaction of test compounds with specific target molecules. However, these methods are generally not highly effective when the test compound binds to or otherwise interacts with its target molecule with moderate or low affinity. In addition, the target molecule may not be readily accessible to a test compound in solution, such as when the target molecule is located inside the cell or within a cellular compartment such as the periplasm of a bacterial cell. Thus, current cell-based assay methods are limited in that they are not effective in identifying or characterizing compounds that interact with their targets with moderate to low affinity or compounds that interact with targets that are not readily accessible.

Cell-based assay methods of the present invention have substantial advantages over current cell-based assays practiced in the art. These advantages derive from the use of sensitized cells in which the level or activity of a

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proliferation-required gene product (the target molecule) has been specifically reduced to the point where the presence or absence of its function becomes a rate-determining step for cellular proliferation. Bacterial, fungal, plant, or animal cells can all be used with the present method. Such sensitized cells become much more sensitive to compounds that are active against the affected target molecule. Thus, cell-based assays of the present invention are capable of detecting compounds exhibiting low or moderate potency against the target molecule of interest because such compounds are substantially more potent on sensitized cells than on non-sensitized cells. The affect may be such that a test compound may be two to several times more potent, at least 10 times more potent or even at least 100 times more potent when tested on the sensitized cells as compared to the non-sensitized cells.

Due in part to the increased appearance of antibiotic resistance in pathogenic microorganisms and to the significant side-effects associated with some currently used antibiotics, novel antibiotics acting at new targets are highly sought after in the art. Yet, another limitation in the current art related to cell-based assays is the problem of identifying hits against the same kinds of target molecules in the same limited set of biological pathways over and over again. This may occur when compounds acting at such new targets are discarded, ignored or fail to be detected because compounds acting at the "old" targets are encountered more frequently and are more potent than compounds acting at the new targets. As a result, the majority of antibiotics in use currently interact with a relatively small number of target molecules within an even more limited set of biological pathways.

The use of sensitized cells of the current invention provides a solution to the above problem in two ways. First, desired compounds acting at a target of interest, whether a new target or a previously known but poorly exploited target, can now be detected above the "noise" of compounds acting at the "old" targets due to the specific and substantial increase in potency of such desired compounds when tested on the sensitized cells of the current invention. Second, the methods used to sensitize cells to compounds acting at a target of interest may also sensitize these cells to compounds acting at other target molecules within the same biological pathway. For example, expression of an antisense molecule to a gene encoding a ribosomal protein is expected to sensitize the cell to compounds acting at that ribosomal protein and may also sensitize the cells to compounds acting at any of the ribosomal components (proteins or rRNA) or even to compounds acting at any target which is part of the protein synthesis pathway. Thus an important advantage of the present invention is the ability to reveal new targets and pathways that were previously not readily accessible to drug discovery methods.

Sensitized cells of the present invention are prepared by reducing the activity or level of a target molecule. The target molecule may be a gene product, such as an RNA or polypeptide produced from the proliferation-required nucleic acids described herein. Alternatively, the target may be a gene product such as an RNA or polypeptide which is produced form a sequence within the same operon as the proliferation-required nucleic acids described herein. In addition, the target may be an RNA or polypeptide in the same biological pathway as the proliferation-required nucleic acids described herein.

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Such biological pathways include, but are not limited to, enzymatic, biochemical and metabolic pathways as well as pathways involved in the production of cellular structures such the cell wall.

Current methods employed in the arts of medicinal and combinatorial chemistries are able to make use of structure-activity relationship information derived from testing compounds in various biological assays including direct binding assays and cell-based assays. Occasionally compounds are directly identified in such assays that are sufficiently potent to be developed as drugs. More often, initial hit compounds exhibit moderate or low potency. Once a hit compound is identified with low or moderate potency, directed libraries of compounds are synthesized and tested in order to identify more potent leads. Generally these directed libraries are combinatorial chemical libraries consisting of compounds with structures related to the hit compound but containing systematic variations including additions, subtractions and substitutions of various structural features. When tested for activity against the target molecule, structural features are identified that either alone or in combination with other features enhance or reduce activity. This information is used to design subsequent directed libraries containing compounds with enhanced activity against the target molecule. After one or several iterations of this process, compounds with substantially increased activity against the target molecule are identified and may be further developed as drugs. This process is facilitated by use of the sensitized cells of the present invention since compounds acting at the selected targets exhibit increased potency in such cell-based assays, thus; more compounds can now be characterized providing more useful information than would be obtained otherwise.

Thus, it is now possible using cell-based assays of the present invention to identify or characterize compounds that previously would not have been readily identified or characterized including compounds that act at targets that previously were not readily exploited using cell-based assays. The process of evolving potent drug leads from initial hit compounds is also substantially improved by the cell-based assays of the present invention because, for the same number of test compounds, more structure-function relationship information is likely to be revealed.

The method of sensitizing a cell entails selecting a suitable gene or operon. A suitable gene or operon is one whose expression is required for the proliferation of the cell to be sensitized. The next step is to introduce into the cells to be sensitized, an antisense RNA capable of hybridizing to the suitable gene or operon or to the RNA encoded by the suitable gene or operon. Introduction of the antisense RNA can be in the form of an expression vector in which antisense RNA is produced under the control of an inducible promoter. The amount of antisense RNA produced is limited by varying the inducer concentration to which the cell is exposed and thereby varying the activity of the promoter driving transcription of the antisense RNA. Thus, cells are sensitized by exposing them to an inducer concentration that results in a sub-lethal level of antisense RNA expression.

In one embodiment of the cell-based assays, the identified exogenous *E. coli* nucleotide sequences of the present invention are used to inhibit the production of a proliferation-required protein. Expression vectors producing antisense RNA against identified genes required for proliferation are used to limit the concentration of a proliferation-required protein without severly inhibiting growth. To achieve that goal, a growth inhibition dose curve of inducer is calculated by plotting

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various doses of inducer against the corresponding growth inhibition caused by the antisense expression. From this curve, various percentages of antisense induced growth inhibition, from 1 to 100% can be determined. If the promoter contained in the expression vector contains a *lac* operator the transcription is regulated by *lac* repressor and expression from the promoer is inducible with IPTG. For example, the highest concentration of the inducer IPTG that does not reduce the growth rate (0% growth inhibition) can be predicted from the curve. Cellular proliferation can be monitored by growth medium turbidity via 0D measurements. In another example, the concentration of inducer that reduces growth by 25% can be predicted from the curve. In still another example, a concentration of inducer that reduces growth by 50% can be calculated. Additional parameters such as colony forming units (cfu) can be used to measure cellular viability.

Cells to be assayed are exposed to the above-determined concentrations of inducer. The presence of the inducer at this sub-lethal concentration reduces the amount of the proliferation required gene product to the lowest amount in the cell that will support growth. Cells grown in the presence of this concentration of inducer are therefore specifically more sensitive to inhibitors of the proliferation-required protein or RNA of interest or to inhibitors of proteins or RNAs in the same biological pathway as the proliferation-required protein or RNA of interest but not to inhibitors of unrelated proteins or RNAs.

Cells pretreated with sub-inhibitory concentrations of inducer and thus containing a reduced amount of proliferation-required target gene product are then used to screen for compounds that reduce cell growth. The sub-lethal concentration of inducer may be any concentration consistent with the intended use of the assay to identify candidate compounds to which the cells are more sensitive. For example, the sub-lethal concentration of the inducer may be such that growth inhibition is at least about 5%, at least about 8%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60% at least about 75%, or more. Cells which are presensitized using the preceding method are more sensitive to inhibitors of the target protein because these cells contain less target protein to inhibit than wild-type cells.

In another embodiment of the cell based assays of the present invention, the level or activity of a proliferation required gene product is reduced using a temperature sensitive ...mutation in the proliferation-required sequence and an antisense nucleic acid against the proliferation-required sequence. Growing the cells at an intermediate temperature between the permissive and restrictive temperatures of the temperature sensitive mutant where the mutation is in a proliferation-required gene produces. The antisense RNA directed against the proliferation-required sequence further reduces the activity of the proliferation required gene product. Drugs that may not have been found using either the temperature sensitive mutation or the antisense nucleic acid alone may be identified by determining whether cells in which expression of the antisense nucleic acid has been induced and which are grown at a temperature between the permissive temperature and the restrictive temperature are substantially more sensitive to a test compound than cells in which expression of the antisense nucleic acid has not been induced and which are grown at a permissive temperature. Also drugs found previously from either the antisense nucleic acid alone or the

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temperature sensitive mutation alone may have a different sensitivity profile when used in cells combining the two approaches, and that sensitivity profile may indicate a more specific action of the drug in inhibiting one or more activities of the gene product.

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Temperature sensitive mutations may be located at different sites within the gene and correspond to different domains of the protein. For example, the dnaB gene of Escherichia coli encodes the replication fork DNA helicase. DnaB has several domains, including domains for oligomerization, ATP hydrolysis, DNA binding, interaction with primase, interaction with DnaC, and interaction with DnaA ((Biswas, E.E. and Biswas, S.B. 1999. Mechanism and DnaB halicase of Escherichia coli: structural domains involved in ATP hydrolysis, DNA binding, and oligomerization. Biochem. 38:10919-10928; Hiasa, H. and Marians, K.J. 1999. Initiation of bidirectional replication at the chromosomal origin is directed by the interaction between helicase and primase. J. Biol. Chem. 274:27244-27248; San Martin, C., Radermacher, M., Wolpensinger, B., Engel, A., Miles, C.S., Dixon, N.E., and Carazo, J.M. 1998. Three-dimensional reconstructions from cryoelectron microscopy images reveal an intimate complex between helicase OnaB and its loading partner OnaC. Structure 6:501-9; Sutton, M.D., Carr, K.M., Vicente, M., and Kaguni, J.M. 1998. Escherichia coli DnaA protein. The Nterminal domain and loading of DnaB helicase at the E. coli chromosomal. J. Biol. Chem. 273:34255-62.), the disclosures of which are incorporated herein by reference in their entireties). Temperature sensitive mutations in different domains of DnaB confer different phenotypes at the restrictive temperature, which include either an abrupt stop or slow stop in DNA replication with or without DNA breakdown (Wechsler, J.A. and Gross, J.D. 1971. Escherichia coli mutents temperaturesensitive for DNA synthesis. Mol. Gen. Genetics 113:273-284, the disclosure of which is incorporated herein by reference in its entirety) and termination of growth or cell death. Combining the use of temperature sensitive mutations in the dnaB

When screening for antimicrobial agents against a gene product required for proliferation, growth inhibition of cells containing a limiting amount of that proliferation-required gene product can be assayed. Growth inhibition can be measured by directly comparing the amount of growth, measured by the optical density of the growth medium, between an experimental sample and a control sample. Alternative methods for assaying cell proliferation include measuring green fluorescent protein (GFP) reporter construct emissions, various enzymatic activity assays, and other methods well known in the art.

gene that cause cell death at the restrictive temperature with an antisense to the dnaB gene could lead to the discovery of

very specific and effective inhibitors of one or a subset of activities exhibited by DnaB.

It will be appreciated that the above method may be performed in solid phase, liquid phase or a combination of the two. For example, cells grown on nutrient agar containing the inducer of the antisense construct may be exposed to compounds spotted onto the agar surface. A compound's effect may be judged from the diameter of the resulting killing zone, the area around the compound application point in which cells do not grow. Multiple compounds may be transferred to agar plates and simultaneously tested using automated and semi-automated equipment including but not restricted to

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multi-channel pipettes (for example the Beckman Multimek) and multi-channel spotters (for example the Genomic Solutions Flexys). In this way multiple plates and thousands to millions of compounds may be tested per day.

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The compounds may also be tested entirely in liquid phase using microtiter plates as described below. Liquid phase screening may be performed in microtiter plates containing 96, 384, 1536 or more wells per microtiter plate to screen multiple plates and thousands to millions of compounds per day. Automated and semi-automated equipment may be used for addition of reagents (for example cells and compounds) and determination of cell density.

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The effectiveness of the above cell based assay was validated using constructs expressing antisense RNA to *E. coli* genes rplL, rplJ, and rplW encoding ribosomal proteins L7/L12, L10 and L23 respectively. These proteins are part of the protein synthesis apparatus of the cell and as such are required for proliferation. These constructs were used to test the effect of antisense expression on cell sensitivity to antibiotics known to bind to the ribosome and thereby inhibit protein synthesis. Constructs expressing antisense RNA to several other genes (elaD, visC, yohH, and aptE/B), the products of which are not involved in protein synthesis were used for comparison.

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First expression vectors containing antisense constructs to either rpIW or to elaD were introduced into separate *E. coli* cell populations. Vector introduction is a technique well known to those of ordinary skill in the art. The expression vectors of this example contain IPTG inducible promoters that drive the expression of the antisense RNA in the presence of the inducer. However, those skilled in the art will appreciate that other inducible promoters may also be used. Suitable expression vectors are also well known in the art. The *E. coli* antisense clones encoding ribosomal proteins L7/L12, L10 and L23 were used to test the effect of antisense expression on cell sensitivity to the antibiotics known to bind to these proteins. First, expression vectors containing antisense to either the genes encoding L7/L12 and L10 or L23 were introduced into separate E. coli cell populations.

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introduced into separate E. coli cell populations.

The cell populations were exposed to a range of IPTG concentrations in liquid medium to obtain the growth

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contained therein. Subsequently, sixteen 200 ul liquid medium cultures were grown in a 96 well microtiter plate at 37 C with a range of IPTG concentrations in duplicate two-fold serial dilutions from 1600 uM to 12.5 uM (final concentration). Additionally, control cells were grown in duplicate without IPTG. These cultures were started from equal amounts of cells

inhibitory dose curve for each clone (Fig. 1). First, seed cultures were grown to a particular turbidity that is measured by

the optical density (OD) of the growth solution. The OD of the solution is directly related to the number of bacterial cells

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derived from the same initial seed culture of a clone of interest. The cells were grown for up to 15 hours and the extent of growth was determined by measuring the optical density of the cultures at 600 nm. When the control culture reached mid-

log phase the percent growth of the control for each of the IPTG containing cultures was plotted against the log concentrations of IPTG to produce a growth inhibitory dose response curve for the IPTG. The concentration of IPTG that inhibits cell growth to 50% (IC_{50}) as compared to the 0 mM IPTG control (0% growth inhibition) was then calculated from

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the curve. Under these conditions, an amount of antisense RNA was produced that reduced the expression levels of rptW and elaD to a degree such that growth was inhibited by 50%.

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Alternative methods of measuring growth are also contemplated. Examples of these methods include measurements of proteins, the expression of which is engineered into the cells being tested and can readily be measured. Examples of such proteins include green fluorescent protein (GFP) and various enzymes.

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Cells were pretreated with the selected concentration of IPTG and then used to test the sensitivity of cell populations to tetracycline, erythromycin and other protein synthesis inhibitors. An example of a tetracycline dose response curve is shown in Figures 2A and 2B for the rpIW and elaD genes, respectively. Cells were grown to log phase and then diluted into media alone or media containing IPTG at concentrations which give 20% and 50% growth inhibition as determined by IPTG dose response curves. After 2.5 hours, the cells were diluted to a final OD600 of 0.002 into 96 well plates containing (1) + /- IPTG at the same concentrations used for the 2.5 hour pre-incubation; and (2) serial two-fold dilutions of tetracycline such that the final concentrations of tetracycline range from 1 µg/ml to 15.6 ng/ml and 0 µg/ml. The 96 well plates were incubated at 37°C and the OD600 was read by a plate reader every 5 minutes for up to 15 hours. For each IPTG concentration and the no IPTG control, tetracycline dose response curves were determined when the control (absence of tetracycline) reached 0.1 OD600. To compare tetracycline sensitivity with and without IPTG, tetracycline IC50s were determined from the dose response curves (Figs. 2A-B). Cells with reduced levels of L23 (rpIW) showed increased sensitivity to tetracycline (Fig. 2A) as compared to cells with reduced levels of elaD (Fig. 2B). Figure 3 shows a summary bar chart in which the ratios of tetracycline IC50s determined in the presence of IPTG which gives 50% growth inhibition versus tetracycline IC50s determined without IPTG (fold increase in tetracycline sensitivity) were plotted. Cells with reduced levels of either L7/L12 (genes rplL, rplJ) or L23 (rp/W) showed increased sensitivity to tetracycline (Fig. 3). Cells expressing antisense to genes not known to be involved in protein synthesis (atpB/E, visC, alaD, yohH) did not show the same increased sensitivity to tetracycline, validating the specificity of this assay (Fig. 3).

In addition to the above, it has been observed in initial experiments that clones expressing antisense RNA to genes involved in protein synthesis (including genes encoding ribosomal proteins L7/L12 & L10, L7/L12 alone, L22, and L18, as well as genes encoding rRNA and Elongation Factor G) have increased sensitivity to the macrolide, erythromycin, whereas clones expressing antisense to the non-protein synthesis genes elaD, atpB/E and visC do not. Furthermore, the clone expressing antisense to rplL and rplJ does not show increased sensitivity to nalidixic acid and ofloxacin, antibiotics which do not inhibit protein synthesis.

The results with the ribosomal protein genes rplL, rplJ, and rplW as well as the initial results using various other antisense clones and antibiotics show that limiting the concentration of an antibiotic target makes cells more sensitive to the antimicrobial agents that specifically interact with that protein. The results also show that these cells are sensitized to antimicrobial agents that inhibit the overall function in which the protein target is involved but are not sensitized to antimicrobial agents that inhibit other functions.

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The cell based assay described above may also be used to identify the biological pathway in which a proliferation-required nucleic acid or its gene product lies. In such methods, cells expressing a sub-lethal level of antisense to a target proliferation-required nucleic acid and control cells in which expression of the antisense has not been induced are contacted with a panel of antibiotics known to act in various pathways. If the antibiotic acts in the pathway in which the target proliferation-required nucleic acid or its gene product lies, cells in which expression of the antisense has been induced will be more sensitive to the antibiotic than cells in which expression of the antisense has not been induced.

As a control, the results of the assay may be confirmed by contacting a panel of cells expressing entisense nucleic acids to many different proliferation-required genes including the target proliferation-required gene. If the antibiotic is acting specifically, heightened sensitivity to the antibiotic will be observed only in the cells expressing antisense to a target proliferation-required gene (or cells expressing antisense to other proliferation-required genes in the same pathway as the target proliferation-required gene) but will not be observed generally in all cells expressing antisense to proliferation-required genes.

Similarly, the above method may be used to determine the pathway on which a test antibiotic acts. A panel of cells, each of which expresses antisense to a proliferation-required nucleic acid in a known pathway, is contacted with a compound for which it is desired to determine the pathway on which it acts. The sensitivity of the panel of cells to the test compound is determined in cells in which expression of the antisense has been induced and in control cells in which expression of the antisense has not been induced. If the test antibiotic acts on the pathway on which an antisense nucleic acid acts, cells in which expression of the antisense has been induced will be more sensitive to the antibiotic than cells in which expression of the antisense has not been induced. In addition, control cells in which expression of antisense to proliferation-required genes in other pathways has been induced will not exhibit heightened sensitivity to the antibiotic. In this way, the pathway on which the test antibiotic acts may be determined.

The Example below provides one method for performing such assays.

EXAMPLE 10

Identification of the Pathway in which a Proliferation-Required

Gene Lies or the Pathway on which an Antibiotic Acts

A. Preparation of Bacterial Stocks for Assay

To provide a consistent source of cells to screen, frozen stocks of host bacteria containing the desired antisense construct are prepared using standard microbiological techniques. For example, a single clone of the organism can be isolated by streaking out a sample of the original stock onto an agar plate containing nutrients for cell growth and an antibiotic for which the antisense construct contains a gene which confers resistance. After overnight growth an isolated colony is picked from the plate with a sterile needle and transferred to an appropriate liquid growth media containing the antibiotic required for maintenance of the plasmid. The cells are incubated at 30°C to 37°C with vigorous shaking for 4 to

A day prior to an assay, a stock vial is removed from the freezer, rapidly thawed (37°C water bath) and a loop of

6 hours to yield a culture in exponential growth. Sterile glycerol is added to 15% (volume to volume) and 100 µL to 500 µL aliquots are distributed into sterile cryotubes, snap frozen in liquid nitrogen, and stored at -80°C for future assays.

B. Growth of Bacteria for Use in the Assay

culture is streaked out on an agar plate containing nutrients for cell growth and an antibiotic to which the antisense construct confers resistance. After overnight growth at 37°C, ten randomly chosen, isolated colonies are transferred from the plate (sterile inoculum loop) to a sterile tube containing 5 mL of LB medium containing the antibiotic to which the antisense vector confers resistance. After vigorous mixing to form a homogeneous cell suspension, the optical density of the suspension is measured at 600 nm (0D600) and if necessary an eliquot of the suspension is diluted into a second tube of 5 mL, sterile, LB medium plus antibiotic to achieve an OD600 \leq 0.02 absorbance units. The culture is then incubated at 37° C for 1-2 hrs with shaking until the OD600 reaches OD 0.2 – 0.3. At this point the cells are ready to be used in the assay.

C. Selection of Media to be Used in Assay

Two fold dilution series of the inducer are generated in culture media containing the appropriate antibiotic for maintenance of the antisense construct. Several media are tested side by side and three to four wells are used to evaluate the effects of the inducer at each concentration in each media. For example, M9 minimal media, LB broth, TBD broth and Muller-Hinton media may be tested with the inducer IPTG at the following concentrations, 50 μ M, 100 μ M, 200 μ M, 400 μ M, 800 μ M and 1000 μ M. Equal volumes of test media inducer and cells are added to the wells of a 384 well microtiter plate and mixed. The cells are prepared as described above and diluted 1:100 in the appropriate media containing the test antibiotic immediately prior to addition to the microtiter plate wells. For a control, cells are also added to several wells of each media that do not contain inducer, for example 0 M IPTG. Cell growth is manitored continuously by incubation at 37°C in a microtiter plate reader monitoring the 0D600 of the wells over an 18-hour period. The percent inhibition of growth produced by each concentration of inducer is calculated by comparing the rates of logarithmic growth against that exhibited by cells growing in media without inducer. The medium yielding greatest sensitivity to inducer is selected for use in the essays described below.

D. Measurement of Test Antibiotic Sensitivity in the Absence of Antisense Construct Induction

 Two-fold dilution series of antibiotics of known mechanism of action are generated in the culture media selected for further assay development that has been supplemented with the antibiotic used to maintain the construct. A panel of test antibiotics known to act on different pathways is tested side by side with three to four wells being used to evaluate the effect of a test antibiotic on cell growth at each concentration. Equal volumes of test antibiotic and cells are added to the wells of a 384 well microtiter plate and mixed. Cells are prepared as described above using the media selected for assay development supplemented with the antibiotic required to maintain the antisense construct and are diluted 1:100 in identical media immediately prior to addition to the microtiter plate wells. For a control, cells are also added to several

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wells that contain the solvent used to dissolve the antibiotics but no antibiotic. Cell growth is monitored continuously by incubation at 37° C in a microtiter plate reader monitoring the OD600 of the wells over an 18-hour period. The percent inhibition of growth produced by each concentration of antibiotic is calculated by comparing the rates of logarithmic growth against that exhibited by cells growing in media without antibiotic. A plot of percent inhibition against log[antibiotic concentration] allows extrapolation of an IC₅₀ value for each antibiotic.

E. Measurement of Test Antibiotic Sensitivity in the Presence of Antisense Construct Inducer

The culture media selected for use in the assay is supplemented with inducer at concentrations shown to inhibit cell growth by 50 and 80% as described above and the antibiotic used to maintain the construct. Two fold dilution series of the panel of test antibiotics used above are generated in each of these media. Several antibiotics are tested side by side with three to four wells being used to evaluate the effects of an antibiotic on cell growth at each concentration, in each media. Equal volumes of test antibiotic and cells are added to the wells of a 384 well microtiter plate and mixed. Cells are prepared as described above using the media selected for use in the assay supplemented with the antibiotic required to maintain the antisense construct. The cells are diluted 1:100 into two 50 mL aliquots of identical media containing concentrations of inducer that have been shown to inhibit cell growth by 50% and 80 % respectively and incubated at 37°C with shaking for 2.5 hours. Immediately prior to addition to the microtiter plate wells, the cultures are adjusted to an appropriate OD₆₀₀ (typically 0.002) by dilution into warm (37°C) sterile media supplemented with identical concentrations of the inducer and antibiotic used to maintain the antisense construct. For a control, cells are also added to several wells that contain solvent used to dissolve test antibiotics but which contain no antibiotic. Cell growth is monitored continuously by incubation at 37°C in a microtiter plate reader monitoring the OD600 of the wells over an 18hour period. The percent inhibition of growth produced by each concentration of antibiotic is calculated by comparing the rates of logarithmic growth against that exhibited by cells growing in media without antibiotic. A plot of percent inhibition against log[antibiotic concentration] allows extrapolation of an IC $_{50}$ value for each antibiotic.

F. Determining the Specificity of the Test Antibiotics

A comparison of the IC_{50} s generated by antibiotics of known mechanism of action under antisense induced and non-induced conditions allows the pathway in which a proliferation-required nucleic acid lies to be identified. If cells expressing an antisense nucleic acid against a proliferation required gene are selectively sensitive to an antibiotic acting via a particular pathway, then the gene against which the antisense acts is involved in the pathway in which the antibiotic acts.

G. Identification of Pathway in which a Test Antibiotic Acts

As discussed above, the cell based assay may also be used to determine the pathway against which a test antibiotic acts. In such an analysis, the pathways against which each member of a panel of antisense nucleic acids acts are identified as described above. A panel of cells, each containing an inducible antisense vector against a gene in a known proliferation-required pathway, is contacted with a test antibiotic for which it is desired to determine the pathway

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on which it acts under inducing an non-inducing conditions. If heightened sensitivity is observed in induced cells expressing antisense against a gene in a particular pathway but not in induced cells expressing antisense against genes in other pathways, then the test antibiotic acts against the pathway for which heightened sensitivity was observed.

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One skilled in the art will appreciate that further optimization of the assay conditions, such as the concentration of inducer used to induce antisense expression and/or the growth conditions used for the assay (for example incubation temperature and media components) may further increase the selectivity and/or magnitude of the antibiotic sensitization exhibited.

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The following example confirms the effectiveness of the methods described above.

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EXAMPLE 11 Identification of the Pathway in which a Proliferation-Required Gene Lies

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Antibiotics of various chemical classes and modes of action were purchased from Sigma Chemicals (St. Louis, MO). Stock solutions were prepared by dissolving each antibiotic in an appropriate aqueous solution based on information provided by the manufacturer. The final working solution of each antibiotic contained no more than 0.2% (w/v) of any organic solvent. To determine their potency against a bacterial strain engineered for expression of an antisense against a proliferation-required 50S ribosomal protein, each antibiotic was serially diluted two or three fold in growth medium supplemented with the appropriate antibiotic for maintenance of the anti-sense construct. At least ten dilutions were prepared for each antibiotic. 25 µL aliquots of each dilution were transferred to discrete wells of a 384-well microplate (the assay plate) using a multi-channel pipette. Quadruplicate wells were used for each dilution of an antibiotic under each treatment condition (plus and minus inducer). Each assay plate contained twenty wells for cell growth controls (growth media replacing antibiotic), ten wells for each treatment (plus and minus inducer, in this example IPTG). Assay plates were usually divided into the two treatments: half the plate containing induced cells and an appropriate concentrations of inducer (in this example IPTG) to maintain the state of induction, the other half containing non-induced cells in the absence of IPTG.

Cells for the assay were prepared as follows. Bacterial cells containing a construct, from which expression of antisense nucleic acid against rplL and rplJ, which encode proliferation-required 50S ribosomal subunit proteins, is inducible in the presence of IPTG, were grown into exponential growth (OD₄₀₀ 0.2 to 0.3) and then diluted 1:100 into fresh media containing either 400 µM or 0 µM inducer (IPTG). These cultures were incubated at 37° C for 2.5 hr. After a 2.5 hr incubation, induced and non-induced cells were respectively diluted into an assay medium at a final OD₆₀₀ value of 0.0004. The medium contained an appropriate concentration of the antibiotic for the maintenance of the anti-sense construct. In addition, the medium used to dilute induced cells was supplemented with 800 µM IPTG so that addition to the assay plate would result in a final IPTG concentration of 400 µM. Induced and non-induced cell suspensions were dispensed (25 µI/well) into the appropriate wells of the assay plate as discussed previously. The plate was then loaded into a plate reader, incubated at constant temperature, and cell growth was monitored in each well by the measurement of

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light scattering at 595 nm. Growth was monitored every 5 minutes until the cell culture attained a stationary growth

phase. For each concentration of antibiotic, a percentage inhibition of growth was calculated at the time point

corresponding to mid-exponential growth for the associated control wells (no antibiotic, plus or minus IPTG). For each antibiotic and condition (plus or minus IPTG), a plot of percent inhibition versus log of antibiotic concentration was generated and the IC50 determined. A comparison of the IC50 for each antibiotic in the presence and absence of IPTG revealed whether induction of the antisense construct sensitized the cell to the mechanism of action exhibited by the antibiotic. Cells which exhibited a significant (standard statistical analysis) numerical decrease in the IC50 value in the presence of inducer were considered to have an increased sensitivity to the test antibiotic.

The results are provided in the table below, which lists the classes and names of the antibiotics used in the

The results are provided in the table below, which lists the classes and names of the antibiotics used in the analysis, the targets of the antibiotics, the IC50 in the absence of IPTG, the IC50 in the presence of IPTG, the concentration units for the IC50s, the fold increase in IC50 in the presence of IPTG, and whether increased sensitivity was observed in the presence of IPTG.

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IABLE IV Expression of Antisense RNA to roll, and roll on Antibiotic Sensitivity

ANTIBIOTIC CLASS INames	TARGET	(C50 (.IPTG)	IC50 (-IPTG) IC50 (+ IPTG)	Conc.	Fold Increase	Sensitivity
				Cuit	in Sensitivity Increased?	Increased?
PROTEIN SYNTHESIS INHIBITOR ANTIBIOTICS						
AMINGGLYCOSIDES						
Gentamicin	30S ribosome function	2715	19 19	lu/uu	141	, ,
Streptomycin	30S ribosome franction	11280	161		Ē	<u>,</u>
Spectinomycin	30S ribasome function	18050	10- /		?	. Tes
Tobramycin	30S ribosome function	3594	70 58		Ü	. is
MACROLIDES		3	00.00	III/Bu	.	Tes
Erythromycin	50S ribosome function	7467	187	- Lujua	ç	,
AROMATIC POYKETIDES			ì			S
Tetracycline	30S ribosome function	199.7	1.83	notus	90	, ,
Minocycline	30S ribosome function	668.4	3.897	Tu/E	122	5 8
Doxycycline	30S ribosome function	413.1	27.81			3 ,
OTHER PROTEIN SYNTHESIS INHIBITORS		:	9:/7		2	
Fusidic acid	Elongation Factor G function	29990	641	fujud	8	\$
Chloramphenicol	30S ribosame function	465.4	1516		3 2	
Lincomycin	50S ribosome function	47150	324.2		146	2 3
OTHER ANTIBIOTIC MECHANISMS		2	7:130		<u>.</u>	 S
B-LACTAMS						
Cefoxitin	Cell wall biosynthesis	2782	2484	jul o	-	
Cefotaxime	Cell wall biosynthesis	243	24 16			2 :
DNA SYNTHESIS INHIBITORS		}	2		_	<u> </u>
Nalidixic acid	DNA Gyrase activity	6973	5025	la la		-
Offoxacin	DNA Gyrase activity	49.61	45.80			2 :
OTHER			, ,		-	2
Bacitracin	Cell membrane function	4077	4677		•	-
Trimethoprim	Dihydrofolate Reductase activity	128.9	181 07		- •	2 :
Vancomycin	Cell wall biosynthesis	145400	72550		- ,	운 :

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The above results demonstrate that induction of an antisense RNA to genes encoding 50S ribosomal subunit proteins results in a selective and highly significant sensitization of cells to antibiotics that inhibit ribosomal function and protein synthesis. The above results further demonstrate that induction of an antisense construct to an essential gene sensitizes an organism to compounds that interfere with that gene products' biological role. This sensitization is restricted to compounds that interfere with pathways associated with the targeted gene and it's product.

Assays utilizing antisense constructs to essential genes can be used to identify compounds that specifically interfere with the activity of multiple targets in a pathway. Such constructs can be used to simultaneously screen a sample against multiple targets in one pathway in one reaction (Combinatorial HTS).

Furthermore, as discussed above, panels of antisense construct containing cells may be used to characterize the point of intervention of any compound affecting an essential biological pathway including antibiotics with no known mechanism of action.

Another embodiment of the present invention is a method for determining the pathway against which a test antibiotic compound is active in which the activity of target proteins or nucleic acids involved in proliferation-required pathways is reduced by contacting cells with a sublethal concentration of a known antibiotic which acts against the target protein or nucleic acid. In one embodiment, the target protein or nucleic acid is a target protein or nucleic acid corresponding to a proliferation-required nucleic acid identified using the methods described above. The method is similar to those described above for determining which pathway a test antibiotic acts against except that rather than reducing the activity or level of a proliferation-required gene product using a sublethal level of antisense to a proliferation-required nucleic acid, the activity or level of the proliferation-required gene product is reduced using sublethal level of a known antibiotic which acts against the proliferation required gene product.

Interactions between drugs which affect the same biological pathway has been described in the literature. For example, Mecillinam (Amdinocillin) binds to and inactivates the penicillin binding protein 2 (PBP2, product of the *mrdA* in *E. coli*). This antibiotic inteacts with other antibiotics that inhibit PBP2 as well as antibiotics that inhibit other penicillin binding proteins such as PBP3 [(Gutmann, L., Vincent, S., Billot-Klein, D., Acar, J.F., Mrena, E., and Williamson, R. (1986) Involvement of penicillin-binding protein 2 with other penicillin-binding proteins in lysis of *Escherichia coli* by some bata-lactam antibiotics alone and in synergistic lytic effect of amdinocillin (mecillinam). Antimicrobial Agents & Chemotherapy, 30:906-912), the disclosure of which is incorporated herein by reference in its entirety]. Interactions between drugs could, therefore, involve two drugs that inhibit the same target protein or nucleic acid or inhibit different proteins or nucleic acids in the same pathway [(Fukuoka, T., Domon, H., Kakuta, M., Ishii, C., Hirasawa, A., Utsui, Y., Ohya, S., and Yasuda, H. (1997) Combination effect between panipenern and vancomycin on highly methicillin-resistant Staphylococcus aureus. Japan. J. Antibio. 50:411-419; Smith, C.E., Foleno, B.E., Barrett, J.F., and Frosc, M.B. (1997) Assessment of the synergistic interactions of levofloxacin and ampicillin against Enterococcus faecium by the checkerboard agar dilution and time-kill methods. Diagnos. Microbiol. Infect. Disease 27:85-92; den Hollander, J.G., Horrevorts, A.M., van Goor, M.L.,

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Verbrugh, H.A., and Mourton, J.W. (1997) Synergism between tobramycin and ceftazidime against a resistant Pseudomonas aeruginosa strain, tested in an in vitro pharmacokinetic model. Antimicrobial Agents & Chemotherapy. 41:95-110), the disclosure of all of which are incorporated herein by reference in their entireties).

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Two drugs may interact even though they inhibit different targets. For example, the proton pump inhibitor, Omeprazole, and the antibiotic, Amoxycillin, two synergistic compounds acting together, can cure Helicobacter pylori infection ((Gabryelewicz, A., Laszewicz, W., Dzieniszewski, J., Ciok, J., Marticz, K., Bielecki, D., Popiela, T., Legutko, J., Knapik, Z., Poniewierka, E. (1997) Multicenter evaluation of dual-therapy (omeprazol and amoxycillin) for Helicobacter pylori-associated duodenal and gastric ulcer (two years of the observation). J. Physiol. Pharmacol. 48 Suppl 4:93-105), the disclosure of which is incorporated herein by reference in its entirety).

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The growth inhibition from the sublethal concentration of the known antibiotic may be at least about 5%, at least about 8%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, or at least about 75%, or more.

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Alternatively, the sublethal concentration of the known antibiotic may be determined by measuring the activity of the target proliferation-required gene product rather than by measuring growth inhibition.

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Cells are contected with a combination of each member of a panel of known antibiotics at a sublethal level and varying concentrations of the test antibiotic. As a control, the cells are contacted with varying concentrations of the test antibiotic alone. The IC50 of the test antibiotic in the presence and absence of the known antibiotic is determined. If the IC50s in the presence and absence of the known drug are substantially similar, then the test drug and the known drug act on different pathways. If the IC₅₀s are substantially different, then the test drug and the known drug act on the same

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> Another embodiment of the present invention is a method for identifying a candidate compound for use as an antibiotic in which the activity of target proteins or nucleic acids involved in proliferation-required pathways is reduced by contacting cells with a sublethal concentration of a known antibiotic which acts against the target protein or nucleic acid. In one embodiment, the target protein or nucleic acid is a target protein or nucleic acid corresponding to a proliferationrequired nucleic acid identified using the methods described above. The method is similar to those described above for identifying candidate compounds for use as antibiotics except that rather than reducing the activity or level of a proliferation-required gene product using a sublethal level of antisense to a proliferation-required nucleic acid, the activity or lavel of the proliferation-required gene product is reduced using a sublethal level of a known antibiotic which acts

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against the proliferation required gene product.

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The growth inhibition from the sublethal concentration of the known antibiotic may be at least about 5%, at least about 8%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, or at least about 75%, or more.

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Alternatively, the sublethal concentration of the known antibiotic may be determined by measuring the activity of the target proliferation-required gene product rather than by measuring growth inhibition.

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In order to characterize test compounds of interest, cells are contacted with a panel of known antibiotics at a sublethal level and one or more concentrations of the test compound. As a control, the cells are contacted with the same concentrations of the test compound alone. The IC_{50} of the test compound in the presence and absence of the known antibiotic is determined. If the IC_{50} of the test compound is substantially different in the presence and absence of the known drug then the test compound is a good candidate for use as an antibiotic. As discussed above, once a candidate compound is identified using the above methods its structure may be optimized using standard techniques such as combinatorial chemistry.

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Representative known antibiotics which may be used in each of the above methods are provided in the table below. However, it will be appreciated that other antibiotics may also be used.

20	ANTIBIOTIC	INHIBITS/TARGET	RESISTANT MUTANTS
	Inhibitors of Transcription		
25	Rifamycin, 1959 Rifampicin Rifabutin Rifaximin	Inhibits initiation of transcription/B-subunit RNA polymerase, rpoB	гров, сгр, суаА
	Streptolydigin	Accelerates transcription chain termination/B- subunit RNA polymerase	тоВ
	Streptovaricin	an acyclic ansamycin, inhibits RNA polymerase	rpoB
	Actinomycin D+EDTA	Intercalates between 2 successive G-C pairs, rpoB, inhibits RNA synthesis	pldA
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	Inhibitors of Nucleic Acid Metab		
	Quinolones, 1962 Nalidixic acid Oxolinic acid	subunit gyrase and/or topoisomerase IV, gyrA	
	CAUMIC ACIO		gyrAorB, icd, sloB
35	Fluoroquinolones Ciprofloxacin,	subunit gyrase, gyrA and/or topoisomerase IV	gyrA
33	1983 Norfloxacin	(probable target in Staph)	norA (efflux in Staph)
	Coumerins Novobiocin	Inhibits ATPase activity of B-subunit gyrase,	
		дугв	gyrB, cysB, cysE, nov, ompA
40	Coumermycin	Inhibits ATPase activity of B-subunit gyrase, gyr8	gyr8, hisW
	Albicidin	DNA synthesis	tsx (nucleoside channel)
	Metronidazole	Causes single-strand breaks in DNA	nar
	Inhibitors of Metabolic Pathways		
45	Sulfonamides, 1932 Sulfanilamide	blocks synthesis of dihydrofolate, dihydro- pteroate synthesis, folP	folP, gpt, pabA, pabB, pabC
	Trimethoprim, 1962	Inhibits dihydrofolate reductase, folA	folA, thyA
	Showdomycin	Nucleoside analogue capable of alkylating	nupC, pnp

5	ANTIBIOTIC	INHIBITS/TARGET	RESISTANT MUTANTS
	Thiolactomycin	sulfhydryl groups, inhibitor of thymidylate synthetase type II fatty acid synthase inhibitor	<i>emrB</i> fadB, emrB due to gena
10	Psicofuranine	Adenosine glycoside antibiotic, target is GMP synthetase	dosage guaA,B
15	Triclosan Diazoborinas Isoniazid, Ethionamida	Inhibits fatty acid synthesis heterocyclic, contains boron, inhibit fatty acid synthesis, enoyl-ACP reductase, fabl	fabi (envM) fabi (envM)
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20	Inhibitors of Translation Phenylpropanoids Chloramphenicol, 1947	Binds to ribosomal peptidyl transfer center preventing peptide translocation/ binds to S6, L3, L6, L14, L16, L25, L26, L27, but preferentially to L16	rm, cmiA, marA, ompF, ompR
	Tetracyclines, 1948, type II polyketides Minocycline Doxycycline	Binding to 30S ribosomal subunit, "A" site on 30S subunit, blocks peptide elongation, strongest binding to S7	clmA (cmr), mar, ompF
25	Macrolides (type I polyketides) Erythromycin, 1950 Carbomycin, Spiramycin	Binding to 50 S ribosomal subunit, 23S rRNA, blocks peptide translocation, L15, L4, L12	rm, rpIC, rpID, rpIV , mac
	etc		
30	Aminoglycosides Streptomycin, 1944 Neomycin	Irreversible binding to 30S ribosomal subunit, prevents translation or causes mistranslation of mRNA/16S rRNA	rpsL, strC,M, ubiF atpA·E, ecfB, hemAC,D,E,G, topA,
	Spectinomycin Kanamycin		rpsC,D,E, rm, spcB atpA-atpE, cpxA, ecfB, hemA,B,L, topA
35	Kasugamycin	·	ksgA,B,C,D, rpiB,K, rpsi,N,M,R
	Gentamicin, 1963 Amikacin Paromycin Lincosamides	Pinding to ED C albanand and a large	rpIF, ubiF cpxA rpsL
40	Lincomycin, 1955 Clindamycin Streptogramins Virginiamycin, 1955 Pristinamycin Synercid: quinupristin /dalfopristin	Binding to 50 S ribosomal subunit, blocks peptide translocation 2 components, Streptogramins A&B, bind to the 50S ribosomal subunit blocking peptide translocation and peptide bond formation	linB, rplN,O, rpsG
45	Fusidanes Fusidic Acid	Inhibition of elongation factor G (EF-G) prevents peptide translocation	fusA
	Kirromycin (Mocimycin)	Inhibition of elongation factor TU (EF-Tu), prevents peptide bond formation	tufA,B

5	ANTIBIOTIC	INHIBITS/TARGET	RESISTANT MUTANTS
·	Pulvomycin Thiopeptin	Binds to and inhibits EF-TU Sulfur-containing antibiotic, inhibits protein synthesis,EF-G	rplE
10	Tiamulin Negamycin	Inhibits protein synthesis Inhibits termination process of protein synthesis	rpiC, rpiD priB
	Oxazolidinones Linezolid Isoniazid	23S rRNA	pdx
15	Nitrofurantoin	Inhibits protein synthesis, nitroreductases convert nitrofurantoin to highly reactive electrophilic intermediates which attack bacterial ribosomal proteins non-specifically	pax nfnA,B
	Pseudomonic Acids Mupirocin (Bactroban)	Inhibition of isoleucyl tRNA synthetase-used for Staph, topical cream, nasal spray	ileS
20	Indolmycin Viomycin	Inhibits tryptophanyl-tRNA synthetase	trpS rmA (23S rRNA methyltransferase; mutant has slow growth rate, slow chain elongation rate, and viomycin resistance)
25	Thiopeptides Thiostrepton Micrococcin	Binds to L11-23S RNA complex Inhibits GTP hydrolysis by EF-G Stimulates GTP hydrolysis by EF-G	
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	Inhibitors of Cell Walls/Membrane B-lactams Penicillin, 1929 Ampicillin	 Inhibition of one or more cell wall transpeptidases, endopeptidases, and 	
35	Methicillin, 1960	glycosidases (PBPs), of the 12 PBPs only 2 are essential: mrdA (PBP2) and ftsl (pbpB, PBP3)	ampC, ampD, ampE, envZ, galU, hipA, hipQ, ompC, ompF, ompR, ptsl, rfa, tolD, tolE
	Cephalosporins, 1962	District the second second second	tonB
40	Mecillinam (amdinocillin) Aztreonam (Furazlocillin)	Binds to and inactivates PBP2 (mrdA) Inactivates PBP3 (ftsI)	alaS, argS, crp, cyaA, envB, mrdA,B, mreB,C,D
	Bacilysin, Tetaine Glycopeptides Vancomycin, 1955	Dipeptide, inhib glucosamine synthase Inhib G+ cell wall syn, binds to terminal D- ala-D-ala of pentapeptide,	dppA
45	Polypeptides Bacitracin Cyclic lipopeptide Daptomycin, 1980	Prevents dephosphorylation and regeneration of lipid carrier Disrupts multiple aspects of membrane	rfa

function, including peptidoglycan synthesis, 5 lipateichoic acid synthesis, and the bacterial mambrane potential Cyclic polypeptides Polymixin, 1939 Surfactant action disrupts cell membrane omrA lipids, binds lipid A micety of LPS Fosfomycin, 1969 Analogue of P-enolpyruvate, inhibits 1st step murA, crp, cyaA glpT, 10 in peptidoglycan synthesis - UDP-NhipA, ptsi, uhpT acetylglucosamine enolpyruvyl transferase, murA. Also acts as immunosuppressant Cycloserine Prevents formation of D-ala dimer, inhibits DhipA, cycA ala ligase, ddlA,B Alafosfalin phosphonodipeptide, cell wall synthesis pepA, tpp 15 inhibitor, potentiator of ·lactams Inhibitors of Protein Processing/Transport Globomycin Inhibits signal peptidase II (cleaves lpp, dnaE prolipoproteins subsequent to lipid modification, IspA 20

EXAMPLE 12

Iransfer of Exogenous Nucleic Acid Sequences to other Bacterial Species Using the E. coli Expression Vectors or Expression Vectors Functional in Bacterial Species other than E. coli.

The above methods were validated using antisense nucleic acids which inhibit the growth of £. coli which were identified using methods similar to those described above. Expression vectors which inhibited growth of E. coli upon induction of antisense RNA expression with IPTG were transformed directly into Enterobacter cloacae, Klabsiella pneumonia or Salmonelle typhimurium. The transformed cells were then assayed for growth inhibition according to the method of Example 1. After growth in liquid culture, cells were plated at various serial dilutions and a score determined by calculating the log difference in growth for INDUCED vs. UNINDUCED antisense RNA expression as determined by the maximum 10 fold dilution at which a colony was observed. The results of these experiments are listed below in Table VI. If there was no effect of antisense RNA expression in an organism, the clone is minus in Table VI. In contrast, a positive in Table VI means that at least 10 fold more cells were required to observe a colony on the induced plate than on the noninduced plate under the conditions used and in that organism.

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Sixteen of the construts were found to inhibit growth in all the organisms tested upon induction of entisense RNA expression with IPTG. Those skilled in the art will appreciate that a negative result in a heterologous organism does not mean that that organism is missing that gene nor does it mean that the gene is unessential. However, a positive result means that the heterologous organism contains a homologous gene which is required for proliferation of that organism. The homologous gene may be obtained using the methods described herein. Those cells that are inhibited by antisense may be used in cell based assays as described herein for the identification and characterization of compounds in order to

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develop antibiotics effective in these organisms. Those skilled in the art will appreciate that an antisense molacule which works in the organism from which it was obtained will not always work in a heterologous organism.

TABLE VI
Sensitivity of Other Microorganisms to Antisense Nucleic Acids That Inhibit Proliferation in E. coff

Mal. No.	S. typhimurium	E. cloacae	K. pneumoniae
EcXA001	+	+	
EcXA004			
EcXA005	+	+	+
EcXA006		•	
EcXA007		+	
EcXA008	+	•	+
EcXA010	+	+	
EcXA011		+	<u> </u>
EcXA012		+	
EcXA013	+	+	
EcXA014	+	+	
EcXA015		+	
EcXA016	+	+	
EcXA017	+	+	+.
EcXA018	+	+	
EcXA019	+	+	
EcXA020	+	+	
EcXA021	+	+	
EcXA023	+	+	
EcXA024	+	•	
EcXA025		•	
EcXA026	+	+	
EcXA027	+	+	
EcXA028	+		<u> </u>
EcXA029	 	-	· · · · · ·

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Mol. No.

EcXA030 EcXA031

EcXA032

EcXA033 EcXA034 EcXA035 EcXA036

EcXA037 EcXA038

EcXA039

EcXA041

EcXA042 EcXA044 EcXA045

EcXA046 EcXA047 EcXA048

EcXA049 EcXA050 EcXA051 EcXA052

EcXA053

EcXA054 EcXA055 S. typhimurium

+

+

+

E. closcae

+

K. pneumoniae

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EXAMPLE 13

Use of Identified Exogenous Nucleic Acid Sequences as Probes

The identified sequence of the present invention can be used as probes to obtain the sequence of additional genes of interest from a second organism. For example, probes to potential bacterial target proteins may be hybridized to nucleic acids from other organisms including other bacteria and higher organisms, to identify homologous sequences. Such

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hybridization might indicate that the protein encoded by the gene to which the probe corresponds is found in humans and therefore not necessarily a good drug target. Alternatively, the gene can be conserved only in bacteria and therefore would be a good drug target for a broad spectrum antibiotic or antimicrobial.

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Probes derived from the identified nucleic acid sequences of interest or portions thereof can be labeled with detectable labels familiar to those skilled in the art, including radioisotopes and non-radioactive labels, to provide a detectable probe. The detectable probe can be single stranded or double stranded and can be made using techniques known in the art, including in vitro transcription, nick translation, or kinase reactions. A nucleic acid sample containing a sequence capable of hybridizing to the labeled probe is contacted with the labeled probe. If the nucleic acid in the sample is double stranded, it can be denatured prior to contacting the probe. In some applications, the nucleic acid sample can be immobilized on a surface such as a nitrocellulose or nylon membrane. The nucleic acid sample can comprise nucleic acids obtained from a variety of sources, including genomic DNA, cDNA libraries, RNA, or tissue samples.

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Procedures used to detect the presence of nucleic acids capable of hybridizing to the detectable probe include well known techniques such as Southern blotting, Northern blotting, dot blotting, colony hybridization, and plaque hybridization. In

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some applications, the nucleic acid capable of hybridizing to the labeled probe can be cloned into vectors such as expression vectors, sequencing vectors, or in vitro transcription vectors to facilitate the characterization and expression of the hybridizing nucleic acids in the sample. For example, such techniques can be used to isolate, purify and clone sequences from a genomic library, made from a variety of bacterial species, which are capable of hybridizing to probes made from the sequences identified

in Examples 5 and 6.

EXAMPLE 14

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Preparation of PCR Primers and Amplification of DNA

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The identified E. coli genes corresponding directly to or located within the operon of nucleic acid sequences required for proliferation or portions thereof can be used to prepare PCR primers for a variety of applications, including the identification or isolation of homologous sequences from other species, for example *S. typhimurium*, *E. cloacee*, and Klebsiella pneumoniae, which contain part or all of the homologous genes. Because homologous genes are related but not identical in sequence, those skilled in the art will often employ degenerate sequence PCR primers. Such degenerate sequence primers are designed based on conserved sequence regions, either known or suspected, such as conserved coding regions. The successful production of a PCR product using degenerate probes generated from the sequences identified herein would indicate the presence of a homologous gene sequence in the species being screened. The PCR primers are at least 10 bases, and preferably at least 20 bases in length. More preferably, the PCR primers are at least 20-30 bases in length. In some embodiments, the PCR primers can be more than 30 bases in length. It is preferred that the primer pairs have approximately the same G/C ratio, so that melting temperatures are approximately the same. A variety of PCR techniques are familiar to those skilled in the art. For a review of PCR technology, see Molecular Cloning to Genetic Engineering White, B.A. Ed. in Methods in Molecular Biology 67: Humana Press, Totowa 1997. When the entire coding sequence of the target gene is known, the 5' and 3' regions of the target gene

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can be used as the sequence source for PCR probe generation. In each of these PCR procedures, PCR primers on either side of the nucleic acid sequences to be amplified are added to a suitably prepared nucleic acid sample along with dNTPs and a thermostable polymerase such as Taq polymerase, Pfu polymerase, or Vant polymerase. The nucleic acid in the sample is denatured and the PCR primers are specifically hybridized to complementary nucleic acid sequences in the sample. The hybridized primers are extended. Thereafter, another cycle of denaturation, hybridization, and extension is initiated. The cycles are repeated multiple times to produce an amplified fragment containing the nucleic acid sequence between the primer sites.

EXAMPLE 15

Inverse PCR

Principles and Applications for DNA Amplification, (Henry A. Erlich, Ed.) W.H. Freeman and Co. (1992). Traditional PCR requires two primers that are used to prime the synthesis of complementary strands of DNA. In inverse PCR, only a core

species of bacteria, a subset of exogenous nucleic sequences are identified that correspond to genes or operons that are required for bacterial proliferation. In species for which a genome sequence is not known, the technique of inverse PCR

provides a method for obtaining the gene in order to determine the sequence or to place the probe sequences in full context to

as to create fragments of nucleic acid that contain the identified sequence as well as unknown sequences that flank the identified sequence. These fragments are then circularized and become the template for the PCR reaction. PCR primers are designed in accordance with the teachings of Example 15 and directed to the ends of the identified sequence are synthesized. The primers direct nucleic acid synthesis away from the known sequence and toward the unknown sequence contained within

the circularized template. After the PCR reaction is complete, the resulting PCR products can be sequenced so as to extend the

sequence of the identified gene past the core sequence of the identified exogenous nucleic acid sequence identified. In this manner, the full sequence of each novel gene can be identified. Additionally the sequences of adjacent coding and noncoding

the target sequence to which the identified exogenous nucleic acid sequence binds.

The technique of inverse polymerase chain reaction can be used to extend the known nucleic acid sequence identified in Examples 5 and 6. The inverse PCR reaction is described generally by Ochman et al., in Ch. 10 of PCR Technology:

Using the sequences identified as relevant from the techniques taught in Examples 5 and 6 and applied to other

To practice this technique, the genome of the target organism is digested with an appropriate restriction enzyme so

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sequence need be known.

regions can be identified.

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EXAMPLE 16

Identification of Genes Required for Staphylococcus aureus Proliferation

Genes required for proliferation in Staphylococcus aureus are identified according to the methods described above.

EXAMPLE 17

Identification of Genes Required for Neisseria gonorrhoeae Proliferation

Genes required for proliferation in Neisseria gonorrhoeae are identified according to the methods described above.

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5		EXAMPLE 18
		Identification of Genes Required for Pseudomonas aeruginosa Proliferation
		Genes required for proliferation in Pseudomonas aeruginosa are identified according to the methods describe
		above.
10	5	EXAMPLE 19
		Identification of Genes Required for Enterococcus faecalis Proliferation
		Genes required for proliferation in Enterococcus faecalis are identified according to the methods described above.
		EXAMPLE 20
15		Identification of Genes Required for Haemophilus influenzae Proliferation
	10	Genes required for proliferation in Haemophilus influenzae are identified according to the methods described above.
		EXAMPLE 21
20		Identification of Genes Required for Selmonella typhimurium Proliferation
20		Genes required for proliferation in Selmonella typhimurium are identified according to the methods described above.
		EXAMPLE 22
	15	Identification of Genes Required for Helicobacter pylori Proliferation
25		Genes required for proliferation in Helicobacter pylori are identified according to the methods described above.
		EXAMPLE 23
		Identification of Genes Required for Mycoplasma pneumoniae Proliferation
		Genes required for proliferation in Mycoplasma pneumoniae are identified according to the methods described
30	20	above.
		EXAMPLE 24
		Identification of Genes Required for Plasmodium ovale Proliferation
		Genes required for proliferation in Plasmodium ovale are identified according to the methods described above.
35		EXAMPLE 25
	25	Identification of Genes Required for Saccharomyces cerevisiae Proliferation
		Genes required for proliferation in Saccharomyces cerevisiae are identified according to the methods described
40		above.
		EXAMPLE 26
		Identification of Genes Required for Entamoeba histolytica Proliferation
	30	Genes required for profiferation in Entamoeba histolytica are identified according to the methods described abova.
45		EXAMPLE 27
		<u>Identification of Genes Required for Candida albicans Proliferation</u>
		Genes required for proliferation in Candida albicans are identified according to the methods described above.
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5			EXAMPLE 28
	,		Identification of Genes Required for Klabsiella pneumoniae Proliferation
			Genes required for proliferation in Klebsiella pneumoniae are identified according to the methods described above.
			EXAMPLE 29
10	5		Identification of Genes Required for Salmonella typhi Proliferation
			Genes required for profiferation in Selmonella typhi are identified according to the methods described above.
			EXAMPLE 3D
45			Identification of Genes Required for Salmonella paratyphi. Proliferation
15			Genes required for proliferation in Salmonella paratyphi are identified according to the methods described above.
	10		EXAMPLE 31
			Identification of Genes Required for Salmonella cholerasuis Proliferation
20			Genes required for proliferation in Salmonella cholerasuis are identified according to the methods described above.
			EXAMPLE 32
			Identification of Genes Required for Stephylococcus epidermis Proliferation
	15		Genes required for proliferation in Staphylococcus epidermis are identified according to the methods described
25		above.	·
			EXAMPLE 33
			Identification of Genes Required for Mycobacterium tuberculosis Proliferation
			Genes required for proliferation in Mycobacterium tuberculosis are identified according to the methods described
30	20	above.	
٠.			EXAMPLE 34
•			Identification of Genes Required for Mycobacterium Jeprae Proliferation
35			Genes required for proliferation in Mycobacterium leprae are identified according to the methods described above.
33			EXAMPLE 35
	25		Identification of Genes Required for Treponema pallidum Proliferation
			Genes required for proliferation in Treponema pallidum are identified according to the methods described above.
40			EXAMPLE 36
			Identification of Genes Required for Bacillus anthracis Proliferation
			Genes required for proliferation in Bacillus anthracis are identified according to the methods described above.
	30		EXAMPLE 37
45			Identification of Genes Required for Yersinia postis Proliferation
			Genes required for proliferation in Yersinia pestis are identified according to the methods described above.

5 **EXAMPLE 38** Identification of Genes Required for Clostridium botulinum Proliferation Genes required for proliferation in Clostridium botulinum are identified according to the methods described above. **EXAMPLE 39** 10 5 Identification of Genes Required for Campylobacter jejuni Proliferation Genes required for proliferation in Campylobacter jajuni are identified according to the methods described above. **EXAMPLE 40** Identification of Genes Required for Chlamydia trachomatis Proliferation 15 Genes required for proliferation in Chlamydia trachomatis are identified according to the methods described above, Use of Isolated Exogenous Nucleic Acid Fragments as Antisense Antibiotics 10 In addition to using the identified sequences to enable screening of molecule libraries to identify compounds useful to identify antibiotics, the sequences themselves can be used as therapeutic agents. Specifically, the identified exogenous 20 sequences in an antisense orientation can be provided to an individual to inhibit the translation of a bacterial target gene. Generation of Antisense Therapeutics from Identified Exogenous Sequences 15 The sequences of the present invention can be used as antisense therapeutics for the treatment of bacterial infections or simply for inhibition of bacterial growth in vitro or in vivo. The therapy exploits the biological process in cells 25 where genes are transcribed into messenger RNA (mRNA) that is then translated into proteins. Antisense RNA technology contemplates the use of antisense oligonucleotides directed against a target gene that will bind to its target and decrease or inhibit the translation of the target mRNA. In one embodiment, antisense oligonucleotides can be used to treat and 30 control a bacterial infection of a cell culture containing a population of desired cells contaminated with bacteria. In 20 another embodiment, the antisense oligonucleotides can be used to treat an organism with a bacterial infection. Antisense aligonucleatides can be synthesized from any of the sequences of the present invention using methods well known in the art. In a preferred embodiment, antisense oligonucleotides are synthesized using artificial means. 35 Uhlmann & Peymann, Chemical Rev. 90:543-584 (1990) review antisense oligonucleotide technology in detail. Modified or 25 unmodified antisense oligonucleotides can be used as therapeutic agents. Modified antisense oligonucleotides are preferred since it is well known that antisense oligonucleotides are extremely unstable. Modification of the phosphate backbones of the antisense oligonucleotides can be achieved by substituting the internucleotide phosphate residues with 40 methylphosphonates, phosphorothioates, phosphoramidates, and phosphate esters. Nonphosphate internucleotide analogs such as siloxane bridges, carbonate brides, thioester bridges, as well as many others known in the art. The preparation of certain entisense oligonucleotides with modified internucleotide linkages is described in U.S. Patent No. 5,142,047, hereby 30 incorporated by reference. 45 Modifications to the nucleoside units of the antisense oligonucleotides are also contemplated. These modifications can increase the half-life and increase cellular rates of uptake for the oligonucleotides in vivo. For example,

a snomeric nucleotide units and modified bases such as 1,2-dideoxy-d-ribofuranose, 1,2-dideoxy-1-phenylribofuranose, and N*, N*-ethano-5-methyl-cytosine are contemplated for use in the present invention.

An additional form of modified antisense molecules is found in peptide nucleic acids. Peptide nucleic acids (PNA) have been developed to hybridize to single and double stranded nucleic acids. PNA are nucleic acid analogs in which the entire deoxyribose-phosphate backbone has been exchanged with a chemically completely different, but structurally homologous, polyamide (peptide) backbone containing 2-aminoethyl glycine units. Unlike DNA, which is highly negatively charged, the PNA backbone is neutral. Therefore, there is much less repulsive energy between complementary strands in a PNA-DNA hybrid than in the comparable DNA-DNA hybrid, and consequently they are much more stable. PNA can hybridize to DNA in either a Watson/Crick or Hoogsteen fashion (Demidov et al., *Proc. Natl. Acad. Sci. U.S.A.*, 92:2637-2641, 1995; Egholm, *Nature* 365:566-568, 1993; Nielsen et al., *Science* 254:1497-1500, 1991; Dueholm et al., *New J. Chem.* 21:19-31, 1997).

Molecules called PNA "clamps" have been synthesized which have two identical PNA sequences joined by a flexible hairpin linker containing three 8-amino-3,6-dioxaoctanoic acid units. When a PNA clamp is mixed with a complementary homopurine or homopyrimidine DNA target sequence, a PNA-DNA-PNA triplex hybrid can form which has been shown to be extremely stable (Bentin et al., *Biochemistry* 35:8863-8869, 1996; Egholm et al., *Nucleic Acids Res.* 23:217-222, 1995; Griffith et al., *J. Am. Chem. Soc.* 117:831-832, 1995).

The sequence-specific and high affinity duplex and triplex binding of PNA have been extensively described (Nielsen et al., Science 254:1497-1500, 1991; Egholm et al., J. Am. Chem. Soc. 114:9677-9678, 1992; Egholm et al., Nature 365:566-568, 1993; Almarsson et al., Proc. Natl. Acad. Sci. U.S.A. 90:9542-9546, 1993; Demidov et al., Proc. Natl. Acad. Sci. U.S.A. 92:2637-2641, 1995). They have also been shown to be resistant to nuclease and protease digestion (Demidov et al., Biochem. Pharm. 48:1010-1313, 1994). PNA has been used to inhibit gene expression (Hanvey et al., Science 258:1481-1485,1992; Nielsen et al., Nucl. Acids. Res., 21:197-200, 1993; Nielsen et al., Gene 149:139-145, 1994; Good & Nielsen, Science, 95: 2073-2076, 1998; all of which are hereby incorporated by reference), to block restriction enzyme activity (Nielsen et al., supre., 1993), to act as an artificial transcription promoter (Mollegaard, Proc. Natl. Acad. Sci. U.S.A., 91:3892-3895, 1994) and as a pseudo restriction endonuclease (Demidov et al., Nucl. Acids. Res. 21:2103-2107, 1993). Recently, PNA has also been shown to have antiviral and antitumoral activity mediated through an antisense mechanism (Norton, Nature Biotechnol., 14:615-619, 1996; Hirschman et al., J. Investig. Med. 44:347-351, 1996). PNAs have been linked to various peptides in order to promote PNA entry into cells (Basu et al., Bioconj. Chem. 8:481-488, 1997; Pardridge et al., Proc. Natl. Acad. Sci. U.S.A., 92:5592-5596, 1995).

The antisense oligonucleotides contemplated by the present invention can be administered by direct application of oligonucleotides to a target using standard techniques well known in the art. The antisense oligonucleotides can be generated within the target using a plasmid, or a phage. Alternatively, the antisense nucleic acid may be expressed from a sequence in the chromosome of the target cell. It is further contemplated that contemplated that the antisense oligonucleotide contemplated are incorporated in a ribozyme sequence to enable the antisense to specifically bind and cleave its

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target mRNA. For technical applications of ribozyme and antisense oligonucleotides see Rossi et al., Pharmacol. Ther. 50(2):245-254, (1991), which is hereby incorporated by reference. The present invention also contemplates using a retron to introduce an antisense oligonucleotide to a cell. Retron technology is exemplified by U.S. Patent No. 5,405,775, which is hereby incorporated by reference. Antisense oligonucleotides can also be delivered using liposomes or by electroporation techniques which are well known in the art.

The antisense nucleic acids of the present invention can also be used to design antibiotic compounds comprising nucleic acids which function by intracellular triple helix formation. Triple helix oligonucleotides are used to inhibit transcription from a genome. The sequences identified as required for proliferation in the present invention, or portions thereof, can be used as templates to inhibit microorganism gene expression in individuals infected with such organisms. Traditionally, homopurine sequences were considered the most useful for triple helix strategies. However, homopyrimidine sequences can also inhibit gene expression. Such homopyrimidine oligonucleotides bind to the major groove at homopurina:homopyrimidine sequences. Thus, both types of sequences based on the sequences of the present invention that are required for proliferation are contemplated for use as antibiotic compound templates.

The antisense oligonucleotides of this example employ the identified sequences of the present invention to induce bacterial cell death or at least bacterial stasis by inhibiting target gene translation. Antisense oligonucleotides containing from about 8 to 40 bases of the sequences of the present invention have sufficient complementary to form a duplex with the target sequence under physiological conditions.

To kill bacterial cells or inhibit their growth, the antisense oligonucleotides are applied to the bacteria or to the target cells under conditions that facilitate their uptake. These conditions include sufficient incubation times of cells and oligonucleotides so that the antisense oligonucleotides are taken up by the cells. In one embodiment, an incubation period of 7-10 days is sufficient to kill bacteria in a sample. An optimum concentration of antisense oligonucleotides is selected for use.

The concentration of antisense oligonucleotides to be used can vary depending on the type of bacteria sought to be controlled, the nature of the entisense oligonucleotide to be used, and the relative toxicity of the antisense oligonucleotide to the desired cells in the treated culture. Antisense oligonucleotides can be introduced to cell samples at a number of different concentrations preferably between 1x10¹⁰M to 1x10⁴M. Once the minimum concentration that can adequately control gene expression is identified, the optimized dose is translated into a dosage suitable for use *in vivo*. For example, an inhibiting concentration in culture of 1x10⁷ translates into a dose of approximately 0.6 mg/kg body weight. Levels of oligonucleotide approaching 100 mg/kg body weight or higher may be possible after testing the toxicity of the oligonucleotide in laboratory animals. It is additionally contemplated that cells from the subject are removed, treated with the antisense oligonucleotide, and reintroduced into the subject. This range is merely illustrative and one of skill in the art are able to determine the optimal concentration to be used in a given case.

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After the bacterial cells have been killed or controlled in a desired culture, the desired cell population may be used for other purposes.

EXAMPLE 41

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The following example demonstrates the ability of an *E. coli* antisense eligonucleotide to act as a bactericidal or bacteriostatic agent to treat a contaminated cell culture system. The application of the antisense eligonucleotides of the present invention are thought to inhibit the translation of bacterial gene products required for proliferation.

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The antisense oligonucleotide of this example corresponds to a 30 base phophorothioate modified oligodeoxynucelotide complementary to a nucleic acid involved in proliferation, such as Molecule Number EcXACO1. A sense oligodeoxynucelotide complementary to the antisense sequence is synthesized and used as a control. The oligonucleotides are synthesized and purified according to the procedures of Matsukura, et al., Gene 72:343 (1988). The test oligonucleotides are dissolved in a small volume of autoclaved water and added to culture medium to make a 100 micromolar stock solution.

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Human bone marrow cells are obtained from the peripheral blood of two patients and cultured according standard procedures well known in the art. The culture is contaminated with the K-12 strain of *E. coli* and incubated at 37°C overnight to establish bacterial infection.

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The control and antisense oligonucleotide containing solutions are added to the contaminated cultures and monitored for bacterial growth. After a 10 hour incubation of culture and oligonucleotides, samples from the control and experimental cultures are drawn and analyzed for the translation of the target bacterial gene using standard microbiological techniques well known in the art. The target *E. coli* gene is found to be translated in the control culture treated with the control oligonucleotide, however, translation of the target gene in the experimental culture treated with the antisense oligonucleotide of the present invention is not detected or reduced.

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EXAMPLE 42

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A subject suffering from an *E. coli* infection is treated with the antisense oligonucleotide preparation of Example 39. The antisense oligonucleotide is provided in a pharmaceutically acceptable carrier at a concentration effective to inhibit the translation of the target gene. The present subject is treated with a concentration of entisense oligonucleotide sufficient to achieve a blood concentration of about 100 micromolar. The patient receives daily injections of antisense oligonucleotide to maintain this concentration for a period of 1 week. At the end of the week a blood sample is drawn and analyzed for the presence or absence using standard techniques well known in the art. There is no detectable evidence of

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E. coli and the treatment is terminated.

EXAMPLE 43

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Preparation and use of Triple Helix Probes

The sequences of microorganism genes required for proliferation of the present invention are scanned to identify 10mer to 20-mer homopyrimidine or homopurine stretches that could be used in triple-helix based strategies for inhibiting gene

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expression. Following identification of candidate homopyrimidine or homopurine stretches, their efficiency in inhibiting gene expression is assessed by introducing varying amounts of oligonucleotides containing the candidate sequences into a population of bacterial cells that normally express the target gene. The oligonucleotides may be prepared on an oligonucleotide synthesizer or they may be purchased commercially from a company specializing in custom oligonucleotide synthesis, such as GENSET, Paris, France.

The oligonucleotides can be introduced into the cells using a variety of methods known to those skilled in the art, including but not limited to calcium phosphate precipitation, DEAE-Dextran, electroporation, liposome-mediated transfection or native uptake.

Treated cells are monitored for a reduction in proliferation using techniques such as monitoring growth levels as compared to untreated cells using optical density measurements. The oligonucleotides that are effective in inhibiting gene expression in cultured cells can then be introduced *in vivo* using the techniques well known in that art at a dosage level shown to be effective.

In some embodiments, the natural (beta) anomers of the oligonucleotide units can be replaced with alpha anomers to render the oligonucleotide more resistant to nucleases. Further, an intercalating agent such as ethidium bromide, or the like, can be attached to the 3 end of the alpha oligonucleotide to stabilize the triple helix. For information on the generation of oligonucleotides suitable for triple helix formation see Griffin et al. (Science 245:967-971 (1989), which is hereby incorporated by this reference).

EXAMPLE 44

Identification of Bacterial Strains from Isolated Specimens by PCR

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Classical bacteriological methods for the detection of various bacterial species are time consuming and costly. These methods include growing the bacteria isolated from a subject in specialized media, cultivation on selective agar media, followed by a set of confirmation assays that can take from 8 to 10 days or longer to complete. Use of the identified sequences of the present invention provides a method to dramatically reduce the time necessary to detect and identify specific bacterial species present in a sample.

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In one exemplary method, bacteria are grown in enriched media and DNA samples are isolated from specimens of, for example, blood, urine, stool, saliva or central nervous system fluid by conventional methods. A panel of PCR primers based on identified sequences unique to various species of microorganisms are then utilized in accordance with Example 12 to amplify DNA of approximately 100-200 bases in length from the specimen. A separate PCR reaction is set up for each pair of PCR primers and after the PCR reaction is complete, the reaction mixtures are assayed for the presence of PCR product. The presence or absence of bacteria from the species to which the PCR primer pairs belong is determined by the presence or absence of a PCR product in the various test PCR reaction tubes.

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Although the PCR reaction is used to assay the isolated sample for the presence of various bacterial species, other assays such as the Southern blot hybridization are also contemplated.

WHAT IS CLAIMED IS:

 A purified or isolated nucleic acid sequence consisting essentially of one of SEQ ID NOs: 405-485, wherein said nucleic acid inhibits microorganism proliferation.

- 2. The nucleic acid sequence of Claim 1, wherein said nucleic acid sequence is complementary to at least a portion of a coding sequence of a gene whose expression is required for microorganism proliferation.
- 3. The nucleic acid sequence of Claims 1 or 2, wherein said nucleic acid comprises a fragment of one of SEQ ID NOs. 405-485, said fragment selected from the group consisting of fragments comprising at least 10, at least 20, at least 25, at least 30, at least 50 or more than 50 consecutive bases of one of SEQ ID NOs: 405-485.
- 4. The nucleic acid sequence of Claim 3, wherein said nucleic acid sequence is complementary to a coding sequence of a gene whose expression is required for microorganism proliferation.
- A vector comprising a promoter operably linked to a nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs. 405-485.
- 6. The vector of Claim 5, wherein said promoter is active in an organism selected from the group consisting of Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa, Enterobacter cloacae, Helicobacter pylori, Neisseria gonorrhoeae, Enterococcus faecalis, Streptococcus pneumoniae, Haemophilus influenzae, Salmonella typhimurium, Saccharomyces cerevisiae, Candida albicans, Cryptococcus neoformans, Aspergillus fumigatus, Klabsiella pneumoniae, Salmonella typhi, Salmonella paratyphi, Salmonella cholerasuis, Staphylococcus epidermidis, Mycobacterium tuberculosis, Mycobacterium leprae, Treponema pallidum, Bacillus anthracis, Yersinia pastis, Clastridium botulinum, campylobacter jejuni, Chlamydia trachomatus, Chlamydia pneumoniae or any species falling within the genera of any of the above species.
 - 7. A host cell containing the vector of Claim 5 or Claim 6.
- 8. A purified or isolated nucleic acid consisting essentially of the coding sequence of one of SEQ ID NOs: 82-88, 90-242.
- 9. A fragment of the nucleic acid of Claim 8, said fragment comprising at least 10, at least 20, at least 25, at least 30, at least 50 or more than 50 consecutive bases of one of SEQ ID NOs: 82-88, 90-242.
 - 10. A vector comprising a promoter operably linked to the nucleic acid of Claim 8 or Claim 9.
- 11. A purified or isolated nucleic acid comprising a nucleic acid sequence complementary to at least a portion of an intragenic sequence, intergenic sequence, sequences spanning at least a portion of two or more genes, 5' noncoding region, or 3' noncoding region within an operon encoding a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs: 243-357, 359-398.
- 12. A purified or isolated nucleic acid comprising a nucleic acid having at least 70% homology to a sequence selected from the group consisting of SEO ID NOs 405-485, 82-88, 90-242 or the sequences complementary thereto as determined using BLASTN version 2.0 with the default parameters.

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5		13.	The nucleic acid of Claim 12, wherein said nucleic acid is from an organism selected from the grou
		consisting of \mathcal{S}_i	aphylococcus aureus, Pseudomonas aeruginosa, Enterobacter cloacae, Helicobacter pylori, Neisseri
		gonorrhoeae, En	terococcus faecalis, Streptococcus pneumoniae, Haemophilus influenzae, Salmonella typhimurium
		Saccharomyces	cerevisiae, Candida albicans, Cryptococcus neoformans, Aspergillus fumigatus, Klebsiella pneumoniae
10	5	Salmonella typhi,	Salmonella paratyphi, Salmonella cholerasuis, Staphylococcus epidermidis, Mycobacterium tuberculosis
		Mycóbacterium .	leprae, Treponema pallidum, Bacillus anthracis, Yersinia pestis, Clostridium botulinum, campylobacte
		jejuni, and Chlan	nydia trachomatus, Chlamydia pneumoniae or any species falling within the genera of any of the abov
		species.	
15		14.	A purified or isolated nucleic acid consisting essentially of a nucleic acid encoding a polypeptide havin
	10	a sequence selec	ted from the group consisting of SEQ ID NOs.: 243-357, 359-398.
		15.	A vector comprising a promoter operably linked to a nucleic acid encoding a polypeptide having
20		sequence selecte	d from the group consisting of SEO ID NOs.: 243-357, 359-398.
20		16.	A host cell containing the vector of Claim 15.
		17.	A purified or isolated polypeptide comprising the sequence of one of SEQ ID NOs: 243-357, 359-388.
	15	18.	A purified or isolated polypeptide comprising a fragment of one of the polypeptides of SEQ ID NOs
25		243-357, 359-39	18, said fragment selected from the group consisting of fragments comprising at least 5, at least 10, a
		least 20, et leas	t 30, at least 40, at least 50, at least 60 or more than 60 consecutive amino acids of one of the
		polypeptides of S	EQ ID NOs.: 243-357, 359-398.
		19.	An antibody capable of specifically binding the polypeptide of Claim 17 or Claim 18.
30	20	20.	A method of producing a polypeptide, comprising introducing a vector comprising a promoter operably
		linked to a nuclei	c acid encoding a polypeptide having a sequence selected from the group consisting of SEQ ID NOs. 243
		357, 359-398inte	o a cell.
		21.	The method of Claim 20, further comprising the step of isolating said protein.
35		22.	A method of inhibiting proliferation comprising inhibiting the activity or reducing the amount of a
	25	polypeptide havin	g a sequence selected from the group consisting of SEO ID NOs. 243-357, 359-398or inhibiting the
		activity or reducin	ig the amount of a nucleic acid encoding said polypeptide.
40		23.	A method for identifying compounds which influence the activity of a polypeptide required for
		proliferation comp	-
			contacting a polypeptide having a sequence selected from the group consisting of 243-357, 359-398
	30	with a c	andidate compound; and
45			determining whether said compound influences the activity of said polypeptide.
		24.	The method of Claim 23, wherein said activity is an enzymatic activity.

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The method of Claim 23, wherein said activity is a carbon compound catabolism activity.

5		26. The method	of Claim 23, wherein said activity is a biosynthetic activity.
		27. The method	of Claim 23, wherein said activity is a transporter activity.
		28. The method of	of Claim 23, wherein said activity is a transcriptional activity.
		29. The method (of Claim 23, wherein said activity is a DNA replication activity.
10	5	30. The method of	of Claim 23, wherein said activity is a cell division activity.
		31. A method fo	r assaying compounds for the ability to reduce the activity or level of a polypeptide
		required for proliferation, compri	sing:
45		providing a ta	arget, wherein said target comprises the coding sequence of a sequence selected from the
15		group consisting of SE	1 ID NOs. 82-88, 90-242;
	10	contacting sa	id target with a candidate compound; and
		measuring an	activity of said target.
20		32. The method (of Claim 31, wherein said target is a messenger RNA molecule transcribed from a coding
		region of one of SEQ ID. NOs.: 8:	2-88, 90-242 and said activity is translation of said messanger RNA.
		33. The method of	of Claim 32, wherein said target is a coding region of one of SEQ ID. NOs. 82-88, 90-242
	15	and said activity is transcription	of said messenger RNA.
25		34. A compound i	dentified using the method of Claim 31.
		35. A method for	identifying compounds which reduce the activity or level of a gene product required for
		cell proliferation comprising the s	teps of:
		expressing ar	antisense nucleic acid against a nucleic acid encoding said gene product in a cell to
30	20	reduce the activity or a	mount of said gene product in said cell, thereby producing a sensitized cell;
		contacting sa	id sensitized cell with a compound; and
		determining v	rhether said compound inhibits the growth of said sensitized cell to a greater extent than
25		said compound inhibits	the growth of a nonsensitized cell.
35		36. The method	of Claim 35, wherein said call is selected from the group consisting of bacterial cells,
	25	fungal cells, plant cells, and anim	al celis.
			f Claim 36, wherein said cell is an <i>E. coli</i> cell.
40			f Claim 36, wherein said cell is from an organism selected from the group consisting of
		Staphylococcus aureus, Pseudo	monas aeruginosa, Enterobacter cloacae, Helicobacter pylori, Neisseria gonorrhoeae,
		Enterococcus faecalis, Streptoc	occus pneumoniae, Haemophilus influenzae, Salmonella typhimurium, Saccharomyces
	30		rptococcus neoformans, Aspergillus fumigatus, Klabsiella pneumoniae, Salmonella typhi,
45			cholerasuis, Staphylococcus epidermidis, Mycobacterium tuberculosis, Mycobacterium
			llus anthracis, Yersinia pastis, Clostridium botulinum, campylobacter jejuni, and Chlamydia
		trachomatus, Chlamydia pnaumor	viae or any species falling within the genera of any of the above species.

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The method of Claim 35, wherein said antisense nucleic acid is transcribed from an inducible promoter. 39. 5 40. The method of Claim 39, further comprising the step of contacting said cell with a concentration of inducer which induces said antisense nucleic acid to a sublethal level. The method of Claim 40, wherein said sub-lethal concentration of said inducer is such that growth 10 5 inhibition is 8% or more. 42. The method of Claim 40, wherein said inducer is isopropyl-1-thio-β-D-galactosida. The method of Claim 35, wherein growth inhibition is measured by monitoring optical density of a 43. culture growth solution. 15 The method of Claim 35, wherein said gene product is a polypeptide. 44. 10 45. The method of Claim 35, wherein said gene product is an RNA. The method of Claim 44, wherein said gene product comprises a polypeptide having a sequence 46. selected from the group consisting of SEQ ID NOs.: 243-357, 359-398. 20 A compound identified using the method of Claim 35. 47. 48. A method for inhibiting cellular proliferation comprising introducing a compound with activity against a gene corresponding to one of SEQ ID NOs.: 82-88, 90-242 or with activity against the product of said gene into a 15 population of calls expressing a gene. 25 The method of Claim 48, wherein said compound is an antisense oligonucleotide comprising a sequence selected from the group consisting of SEQ ID NOs.: 405-485, or a proliferation-inhibiting portion thereof. The method of Claim 49, wherein said proliferation inhibiting portion of one of SEQ ID NOs. 405-485 is 20 30 a fragment comprising at least 10, at least 20, at least 25, at least 30, at least 50 or more than 50 consecutive bases of one of SEQ ID NOs: 405-485. 51. The method of Claim 48, wherein said compound is a triple helix oligonucleotide. A preparation comprising an effective concentration of an antisense oligonucleotide comprising a 35 sequence selected from the group consisting of SEQ ID NOs.: 405-485, or a proliferation-inhibiting portion thereof in a 25 pharmaceutically acceptable carrier. The preparation of Claim 52, wherein said proliferation-inhibiting portion of one of SEQ ID NOs. 405-485 comprises at least 10, at least 20, at least 25, at least 30, at least 50 or more than 50 consecutive bases of one of 40 SEQ ID NOs: 405-485. A method for inhibiting the expression of a gene in an operon required for proliferation comprising 30 contacting a cell in a cell population with an antisense nucleic acid, said cell expressing a gene corresponding to one of SEQ ID NOs.: 82-88, 90-242, wherein said antisense nucleic acid comprises at least a proliferation-inhibiting portion of 45 said operon in an antisense orientation that is effective in inhibiting expression of said gene.

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5		55.	The method of Claim 54, wherein said antisense nucleic acid is complementary to a sequence of a gent
		comprising one o	r more of SEQ ID NOs.: 82-88, 90-242.
		56.	The method of Claim 54, wherein said antisense nucleic acid is a sequence of one of SEQ ID NOs.: 405
		485, or a portion	thereof.
10	5	57.	The method of Claim 54, wherein said cell is contacted with said antisense nucleic acid by introducing
		a plasmid which	expresses said antisense nucleic acid into said cell population.
		58.	The method of Claim 54, wherein said cell is contacted with said antisense nucleic acid by introducing
		a phage which ex	presses said antisense nucleic acid into said cell population.
15		59.	The method of Claim 54, wherein said cell is contacted with said antisense nucleic acid by introducing
	10	a sequence enco	ding said antisense nucleic acid into the chromosome of said cell into said cell population.
		60.	The method of Claim 54, wherein said cell is contacted with said antisense nucleic acid by introducing
20		a retron which e	presses said antisense nucleic acid into said cell population.
		61.	The method of Claim 54, wherein said cell is contacted with said antisense nucleic acid by introducing
		a ribozyme into	said call-population, wherein a binding portion of said ribozyme is complementary to said antisense
	15	oligonucleotide.	
25		62.	The method of Claim 54, wherein said cell is contacted with said antisense nucleic acid by introducing
		a liposome comp	rising said antisense oligonucleotide into said cell.
		63.	The method of Claim 54, wherein said cell is contacted with said antisense nucleic acid by
		electroporation.	•
30	20	64.	The method of Claim 54, wherein said entisense nucleic acid is a fragment comprising at least 10, at
		least 20, at least	25, at least 30, at least 50 or more than 50 consecutive bases of one of SEO ID NOs: 82-88, 90-242.
		65.	The method of Claim 54 wherein said antisense nucleic acid is an oligonucleotide.
		66.	A method for identifying bacterial strains comprising the steps of:
35			providing a sample containing a bacterial species; and
	25		identifying a bacterial species using a species specific probe having a sequence selected from the group
		consist	ng of SEQ ID NOs. 405-485, 82-88, 90-242.
40		67.	A method for identifying a gene in a microorganism required for proliferation comprising:
70			(a) identifying an inhibitory nucleic acid which inhibits the activity of a gene or gene product
		required	for proliferation in a first microorganism;
	30		(b) contacting a second microorganism with said inhibitory nucleic acid;
45			(c) determining whether said inhibitory nucleic acid from said first microorganism inhibits
		prolifera	ation of said second microorganism; and

5			(d)	identifying the gene in said second microorganism which is inhibited by said inhibitory nucleic
		acid.		
		68.	A meth	od for assaying a compound for the ability to inhibit proliferation of a microorganism comprising:
			(a)	identifying a gene or gene product required for proliferation in a first microorganism;
10	5		(b)	identifying a homolog of said gene or gene product in a second microorganism;
			(c)	identifying an inhibitory nucleic acid sequence which inhibits the activity of said homolog in
		said se	cond micro	oorgansim;
			(d)	contacting said second microorganism with a proliferation-inhibiting amount of said inhibitory
15		nucleic	acid, thus	sensitizing said second microorganism;
	10		(a)	contacting the sensitized microorganism of step (d) with a compound; and
			(f)	determining whether said compound inhibits proliferation of said sensitized microorganism to
20		a great	er extent 1	than said compound inhibits proliferation of a nonsensitized microorganism.
		69.	The me	thod of Claim 68, wherein said step of identifying a gene involved in proliferation in a first
		microorganism co	omprises:	
	15		introdu	cing a nucleic acid comprising a random genomic fragment from said first microorganism
25		operabl	ly linked to	o a promoter wherein said random genomic fragment is in the antisense orientation; and
			compar	ing the proliferation of said first microorganism transcribing a first level of said random genomic
		fragme	nt to the	proliferation of said first microorganism transcribing a lower level of said random genomic
		fragme	nt, where	in a difference in proliferation indicates that said random genomic fragment comprises a gene
30	20	involve	d in prolife	ration.
		70.	The me	ethod of Claim 69, wherein said step of identifying a homolog of said gene in a second
		microorganism co	omprises i	dentifying a homologous nucleic acid or a nucleic acid encoding a homologous polypeptide in a
35		database using a	in algorith	m selected from the group consisting of BLASTN version 2.0 with the default parameters and
33		FASTA version 3	•	orithm with the default parameters.
	25	71.		ethod of Claim 69, wherein said step of identifying a homolog of said gene in a second
		microorganism c	omprises i	dentifying a homologous nucleic acid or a nucleic acid encoding a homologous polypeptide by
40			c acids w	hich hybridize to said first gene.
		72.	The me	ethod of Claim 69, wherein the step of identifying a homolog of said gene in a second
		microorganism c	omprises	expressing a nucleic acid which inhibits the proliferation of said first microorganism in said
	30	second microarga	anism.	
45		73.	The me	thod of Claim 69, wherein said inhibitory nucleic acid is an antisense nucleic acid.
		74.		thod of Claim 69, wherein said inhibitory nucleic acid comprises an antisense nucleic acid to a
	•	portion of said ho	molog.	

5		75.	The method of Claim 69, wherein said inhibitory nucleic acid comprises an antisense nucleic acid to a
		portion of the op	peron encoding said homolog.
		. 76.	The method of Claim 69, wherein the step of contacting the second microorganism with a proliferation-
		inhibiting amoun	t of said nucleic acid sequence comprises directly contacting said second microorganism with said nucleic
10	5	acid.	
		77.	The method of Claim 69, wherein the step of contacting the second microorganism with a proliferation-
		inhibiting amoun	nt of said nucleic acid sequence comprises expressing an antisanse nucleic acid to said homolog in said
		second microorg	anism.
15		78.	A compound identified using the method of Claim 68.
	10	79.	A method of assaying a compound for the ability to inhibit proliferation comprising:
			(a) identifying an inhibitory nucleic acid sequence which inhibits the activity of a gene or gene
20		. produc	t required for proliferation in a first microorgansim;
			(b) contacting a second microorganism with a proliferation-inhibiting amount of said inhibitory
		nucleic	acid, thus sensitizing said second microorganism;
	15		(c) contacting the proliferation-inhibited microorganism of step (b) with a compound; and
25			(d) determining whether said compound inhibits proliferation of said sensitized second
		microorganism to	a greater extent than said compound inhibits proliferation of a nonsensitized second microorganism.
		80.	· The method of Claim 79, wherein said inhibitory nucleic acid is an antisense nucleic acid which inhibits
		the proliferation	of said first microorganism.
30	20	81.	The method of Claim 79, wherein said inhibitory nucleic acid comprises a portion of an antisense
		nucleic acid whic	h inhibits the proliferation of said first microorganism.
		82.	The method of Claim 79, wherein said inhibitory nucleic acid comprises an antisense molacule against
		the entire coding	region of the gene involved in proliferation of the first microorganism.
35		83.	The method of Claim 79, wherein said inhibitory nucleic acid comprises an antisense nucleic acid to a
	25	portion of the op	eron encoding the gene involved in proliferation of the first microorganism.
		84.	A compound identified using the method of Claim 79.
40		85.	A method for assaying compounds for activity against a biological pathway required for proliferation
		comprising:	
			sensitizing a cell by expressing an antisense nucleic acid against a nucleic acid encoding a gene product
	30	required	for proliferation in a cell to reduce the activity or amount of said gene product;
45			contacting the sensitized cell with a compound; and
			determining whether said compound inhibits the growth of said sensitized cell to a greater extent than
		said cor	npound inhibits the growth of an nonsensitized cell.

86. The method of Claim 85, wherein said cell is selected from the group consisting of bacterial cells, 5 fungal cells, plant cells, and animal cells. 87. The method of Claim 86, wherein said cell is an E. coli cell. 88. The method of Claim 85, wherein said cell is from an organism selected from the group consisting of 10 5 Staphylococcus aureus, Pseudomonas aeruginosa, Enterobacter cloacae, Halicobacter pylori, Neissaria gonorrhoeae, Enterococcus faecalis, Streptococcus pneumoniae, Haemophilus influenzae, Salmonella typhimurium, Saccharomyces cerevisiae, Candida albicans, Cryptococcus neoformans, Aspergillus fumigatus, Klebsiella pneumoniae, Salmonella typhi, Salmonella paratyphi, Salmonella cholerasuis, Staphylococcus epidermidis, Mycobacterium tuberculosis, Mycobacterium 15 leprae, Treponema pallidum, Bacillus anthracis, Yersinia pestis, Clostridium botulinum, campylobacter jejuni, and Chlamydia 10 trachomatus, Chlamydia pneumoniae or any species falling within the genera of any of the above species. 89. The method of Claim 85, wherein said antisense nucleic acid is transcribed from an inducible promoter. The method of Claim 89, further comprising contacting the cell with an agent which induces expression 90. 20 of said antisense nucleic acid from said inducible promoter, wherein said antisense nucleic acid is expressed at a sublethal level. 15 91. The method of Claim 90, wherein said sublethal level of said antisense nucleic acid inhibits proliferation by 8% or more. 25 92. The method of Claim 90, wherein said agent is isopropyl-1-thio·β-D-galactoside (IPTG). 93. The method of Claim 91, wherein inhibition of proliferation is measured by monitoring the optical density of a liquid culture. 30 20 The method of Claim 85, wherein said gene product comprises a polypeptide having a sequence 94. selected from the group consisting of SEQ ID NOs: 243-357, 359-398. 95. A compound identified using the method of Claim 85. 96. A method for assaying a compound for the ability to inhibit cellular proliferation comprising: 35 contacting a cell with an agent which reduces the activity or level of a gene product required for 25 proliferation of said cell; contacting said cell with said compound; and determining whether said compound reduces proliferation to a greater extent than said compound 40 reduces proliferation of cells which have not been contacted with said agent. The method of Claim 96, wherein said agent which reduces the activity or level of a gene product required for proliferation of said cell comprises an antisense nucleic acid to a gene or operon required for proliferation. 30 The method of Claim 96, wherein said agent which reduces the activity or level of a gene product 45 required for proliferation of said cell comprises an antibiotic.

5		99. The method of Claim 96, wherein said cell contains a temperature sensitive mutation which reduces the
		activity or level of said gene product required for proliferation of said cell.
		100. The method of Claim 99, wherein said antisense nucleic acid is directed against the nucleic acid
		encoding the same functional domain of said gene product required for proliferation of said cell to which said antisense
10	5	nucleic acid is directed.
		101. The method of Claim 99, wherein said antisense nucleic acid is directed against the nucleic acid a
,		different functional domain of said gene product required for proliferation of said cell than the functional domain to which
		said antisense nucleic acid is directed.
15		102. A compound identified using the method of Claim 96.
	10	103. A method for identifying the pathway in which a proliferation-required nucleic acid or its gene product
		lies comprising:
20		expressing a sublethal level of an antisense nucleic acid directed against said proliferation-required nucleic acid in
20		a cell;
		contacting said cell with an antibiotic, wherein the biological pathway on which said antibiotic acts is known;
	15	and
25		determining whether said cell has a substantially greater sensitivity to said antibiotic than a cell which does not
		express said sublethal level of said antisense nucleic acid.
		104. A method for determining the pathway on which a test compound acts comprising:
		(a) expressing a sublethal level of an antisense nucleic acid directed against a proliferation-required nuclaic acid in
30	20	a cell, wherein the biological pathway in which said proliferation-required nucleic acid lies is known,
		(b) contacting said cell with said test compound; and
		(c) determining whether said cell has a substantially greater sensitivity to said test compound than a cell which
0.5		does not express said sublethal level of said antisense nucleic acid.
35		105. The method of Claim 104, further comprising:
	25	(d) expressing a sublethal level of a second antisense nucleic acid directed against a second
		proliferation-required nucleic acid in said cell, wherein said second proliferation-required nucleic acid is in a
40		different biological pathway than said proliferation-required nucleic acid in step (a); and
		(e) determining whether said cell has a substantially greater sensitivity to said test compound than a
		cell which does not express said sublethal level of said second antisense nucleic acid.
	30	106. A purified or isolated nucleic acid consisting essentially of one of SEQ ID NOs: 358, 399-402.
45		107. A compound identified using the method of Claim 23.
		108. A compound which interacts with the gene or gene product of a nucleic acid comprising a sequence of
		one of SEQ ID NOs: 82-88, 90-242 to inhibit proliferation.

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5		inhibit pro	109. oliferation	A compound which interacts with a polypeptide comprising one of SEQ ID NOs. 243-357, 359-398 to
		proliferat	110. ion.	A compound which interacts with a nucleic acid comprising one of SEQ ID NOs: 358, 399-402 to inhibit
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30				
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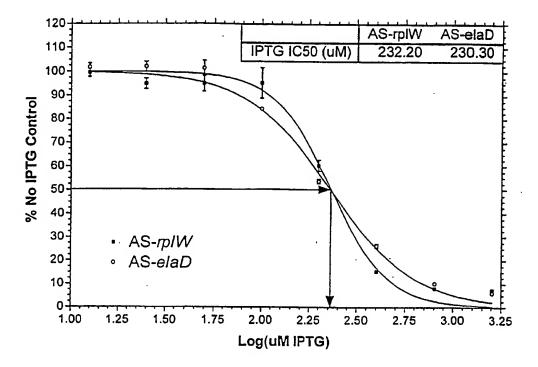


Fig. 1

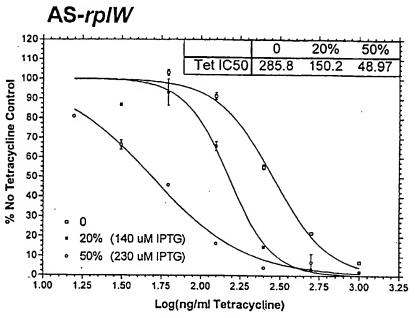


Fig. 2a

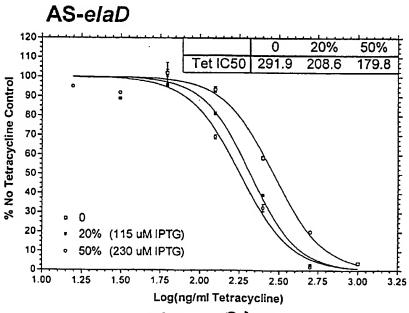
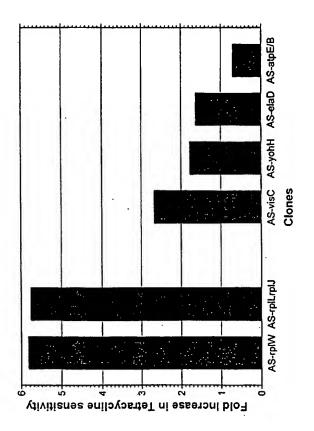


Fig. 2b



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cgaggatttt agaatggctg aaattaccgc atccctggta aaagagctgc gtgagcgtac
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tggcgcaggc atgatggatt gcaaaaaagc actgactgaa gctaacggcg acatcgagct
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ggcaatcgaa aacatgcgta agtccggtgc tattaaagca gcgaaaaaag caggcaacgt
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tgctgctgac ggcgtgatca aaaccaaaat cgacggcaac tacggcatca ttctggaagt
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taactgccag actgacttcg ttgcaaaaga cgctggtttc caggcgttcg cagacaaagt tctggacgca gctgttgctg gcaaaatcac tgacgttgaa gttctgaaag cacagttcga
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ttgctgctaa aagcgctgac gaagaactgg ttaaacacat cgttttgacc tttgttgcaa
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                                                                      PCT/US00/02200
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ttgata
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totaccaggt ctttagcttc tttcagaccc aggccagttg cgccacgtac tgctttgata
                                                                             180
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                                                                              60
                                                                             120
cggagagttc ggcgctttgg attncgcaac gtcagccatt accgcagcgt cgtactgcag
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cggaccggcg atcatcaggt ca
                                                                             202
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      <211> 261
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gcaaacttct cgccatcaaa tagcccctga ctggttagtt ttagcgcggg gatcactggc
                                                                             180
agagaaagaa acgccatctg aataaacggc tcatcgggta acggaccgca ttcacgggcg
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480

540 600

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acgggagcta ttaaataaaa tatgcattgt ttcaatgctg gctcgtttac gtctgatgcc aaaaggatgt gcacaatgaa ttcagcattt gtgcttgttc tgacagtttt tcttgtttcc

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                                                                 PCT/US00/02200
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attgttaact ggttaacgtc acctggaggc accaggcact gcatcacaaa attcattgtt
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gaggacgcga taatgaaaac gttattacca aacgttaata cgtctgaagg ttgttttgaa
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attggtgtca ctatcagtaa cccagtattt actgaagatg ccattaacaa gagaaaacaa
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gaacgggagc tattaaataa aatatgcatt gtttcaatgc tggctcgttt acgtctgatg
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ccaaaaggat gtgcacaatg aattcagcat ttgtgcttgt tctgacagtt tttcttgttt
                                                                        420
ccggagagec agttgatatt gcagtcagtg ttcacaggac aatgcangag tgtatgactg
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cagcaacccg aacagaaaat toocggtaac tgttacccgg tcgataaagt tattcaccag
                                                                        540
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      <213> E. Coli
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cgaggtgcag ttcgcccata cccgcgatga tggtctggtt agattcttcg tcagtccata
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cacggaaaga cgggtettet ttagccagae ggcccagage cagacccatt ttttectggt
                                                                       240
cagetttggt tttcggttca actgcgatgg agattaccgg ctcagggaat tccatacgtt
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ccagaatgat cggcgcatcc gggtcacaca gggtgtcacc agtggttacg tctttcagac
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cgatagcagc agcgatgtcg cccgcgcgaa cttctttgat ctcttcacgt ttgttagcgt
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gaatacccat gtctactacc gggtagcctg ccagcggacc tgcttcagc tgttcctgga
                                                                       180
tacctttatc aacggccggg atgtattcgc cagggattac accaccttta atgtcgttga
                                                                       240
tgaactcgta gcctttcggg tttgaacccg gctccagcgg gtacatgtcg ataacaacat
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gaccatactg accacgacca ccagactgtt tcgcgtgttt accttcaaca tcggtaactt
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attcacgett catacggtca acgatgatgt cgaggtgcag ttcgcccata cccgcgatga
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tggtctggtt agattetteg teagtecata caeggaaaga egggtettet ttagecagae
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gggccanagc cagacccatt ttttcctggt cagctttggt tttcggtcaa ctgcgatgga
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gattaccggc tcanggaatt tccatacctt ccaggaatga tcggcgcatt ccggtcaaac
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anggngtacc aggggggtac ntntttttaa nancgattgc cagcancgga tntnncccgn
                                                                       720
geenaactte tttggaaenn tttaceggtt ggtaacenge ettttnaaen atecaacega
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cgccagggat tacaccacct ttaatgtcgt tgatgaactc gtagcctttc gggtttgaac
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ctgatcette tgttettata acacaaggaa acgtaettaa ggtgeegtee ggtgaaceag
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toggacgcac ctttaataac tataaataag tgtctgggca gatactatat aaattaactt
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 gtgctgatcc atccgccgac tacggcaccg actatcccca gcaggatagt cataaagaat
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ccacctccat ctttacctgg catgatccac ttcgccagaa taccggcaat aagcccaaaa
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                                                                          540
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cacttcaage eggeacttet ggeaceagea aagteategg egtetetggt teataatega
                                                                          720
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gegeetgatg aategegtta teaategetg cettaegege tttgtettta taggeateeg
                                                                          360
gctgcgccac gcccagcgac acagaacgaa tt
                                                                          392
      <210> 31
      <211> 351
      <212> DNA
      <213> E. Coli
      <400> 31
ctatccttga tgaaaccgcg agcaaagata ggtgattacg tcatggtttt acagaaaatt
acagaaaaag gaggcaatat cgggtaaagg cattagcccg acgaatacgt cgggctacaa
                                                                          120
atattattgt gctgcaggtg ttttagcggg ttgttgatcc acaggttcta actggaagac
                                                                          180
cacategace tgateateaa actgaatage ggeetgeteg taagttteet gggeggacae
                                                                          240
cggcgcgca tcggctttca tcatccgcac cattgggctg ggctgatagt tggaaacatg
                                                                         300
gtagcgcacg ctatataccg gccccagttt acgatgaaag ccgttcgcca g
                                                                         351
      <210> 32
      <211> 762
    · <212> DNA
      <213> E. Coli
      <220>
      <221> misc_feature
      <222> (1) ... (762)
      <223> n = A, T, C or G
      <400> 32
aattatgaaa cactgtctgg aatcgtctga atgacgggca catttgcgag cacgcatcca
```

PCT/US00/02200

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gtaataacac aggaaactat tttatctacg cgttagcgat agactgcttg catggcgaaa
ggaggtmagc cgacgatttc agcgggacgc tgamacggga aagcccctcc cgaggaaggg
                                                                        180
gccataaata aggaaagggt catgatgaag ctactcatca tcgtggtgct cttagtcata
                                                                        240
agettecceg ettactaaga etaceaggge gggggaaace eegetetace eteacteetg
                                                                        300
aaagtatgcc ttcacgataa gattgtcaat ccgcaggctt tgtagtctgc gatcctgcca
                                                                        360
gcaaatattc tttgcgagtc gttacgcaat aatcacagag gaaactattt tattcacgcg
                                                                        420
ttagcgatag actgcattca gggcgaaagg aggtaagccg atgatttcag cgggacgctg
                                                                        480
aaacgggaaa gcctctcccg gagaagaggg cttttaataa ggaaagggtt atgatgaagc
                                                                       540
acgtcatcat actggtgata ctcttagtga ttagcttcca ggcttactaa gaacaccagg
                                                                        600
gggagggga aacctcttcc taaccctcac ttctgaaatt gggtgctatg acgctggcgt
                                                                       660
tactgcttan cgctaccagt ttgtctgccc tggcggttgt aacgccagat cggtacccgt
                                                                       720
ttggatattt taatgaaagc cgacaaatca atcancgtga cg
                                                                       762
      <210> 33
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      <212> DNA
      <213> E. Coli
gcacatttgc gagcacgcat ccagtaataa cacaggaaac tattttatct acgcgttagc
                                                                        60
gatagactgc ttgcatggcg aaaggaggta agccgacgat ttcagcggga cgctgaaacg
                                                                       120
ggaaagcccc tcccgaggaa ggggccataa ataaggaaag ggtcatgatg aagctactca
                                                                       180
tcatcgtggt gctcttagtc ataagcttcc ccgcttacta agactaccag ggcgggggaa
                                                                       240
accongetet acceteacte etgaaagtat geetteacga taagattgte aat
                                                                       293
      <210> 34
      <211> 633
      <212> DNA
      <213> E. Coli
      <220>
      <221> misc_feature
      <222> (1) ... (633)
      <223> n = A, T, C or G
      <400> 34
atttacactt tttacgaaat catgggatca ctaacaaaat atcgcttgtc agttatattg
tatggcagga aagatatgcg actgatatta cagatcccca aagtggagag tttatgacca
                                                                       120
ttaaaaataa gatgttgctg ggtgcgcttt tgctggttac cagtgccgcc tqqqccqcac
                                                                       180
cagocaccgc gggttcgacc aatacctcgg gaatttctaa gtatgagtta agtagtttca
                                                                       240
ttgctgactt taagcatttc aaaccagggg acaccgtacc agaaatgtac cgtaccgatg
                                                                       300
agtacaacat taagcagtgg cagttgcgta acctgcccgc gcctgatgcc gggacgcact
                                                                       360
ggacctatat gggtggcgcg tacgtgttga tcagcgacac cgacggtaaa atcattaaag
                                                                       420
cctacgacgg tgagattttt tatcatcgct aaaaaaaagcc ccctcatcat gagggggaaa
                                                                       480
tgcagacacc ttgntatttt ttattattag ccacttgctc gtcttgcttg gtattaagtc
                                                                       540
gtattcacg ttgattaatg enggtggete eagtgegeea gattaacttt gtttggateg
                                                                       600
aagacgtagt aactggctgg ttatcggaat tgg
                                                                       633
      <210> 35
      <211> 569
      <212> DNA
      <213> E. Coli
      <400> 35
tatggcagga aagatatgcg actgatatta cagatcccca aagtggagag tttatgacca
                                                                        60
ttaaaaataa gatgttgctg ggtgcgcttt tgctggttac cagtgccgcc tgggccgcac
                                                                       120
cagccaccgc gggttcgacc aatacctcgg gaatttctaa gtatgagtta agtagtttca
                                                                       180
ttgctgactt taagcatttc aaaccagggg acaccgtacc agaaatgtac cgtaccgatg
                                                                       240
agtacaacat taagcagtgg cagttgcgta acctgcccgc gcctgatgcc gggacgcact
                                                                       300
ggacctatat gggtggcgcg tacgtgttga tcagcgacac cgacggtaaa atcattaaag
                                                                       360
cctacgacgg tgagattttt tatcatcgct aaaaaaagcc ccctcatcat gagggggaaa
                                                                       420
```

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tgcagacacc ttgttatttt ttattattag ccacttgctc gtcttgcttg ttattagtcg
                                                                       480
tatttcacgt tgattaatgc ggttgcctcc agtgcgccag atttaacttt gtttgtatcg
                                                                       540
tagacgtagt aactggctgg tatcggaat
                                                                       569
      <210> 36
      <211> 338
      <212> DNA
      <213> E. Coli
      <400> 36
cgtattcaca tccttttgat tggtgataac atgcgaatcg gtattatttt tccggttgta
                                                                        60
atotteatta cageggtegt atttttagea tggtttttta ttggeggeta tgetgeeceg
                                                                       120
ggagcataaa gatgaaaaaa acaacgatta ttatgatggg tgtggcgatt attgtcgtac
                                                                       180
tcggcactgc ctgggatggt ggtaacgtca cctctaaaaa atagcaaagg ctgcctgtgt
                                                                       240
gcagcctttg tgcaatttaa gcgttaactt ttaatcttcc tgtagataaa tagcacgaca
                                                                       300
atogoaccaa taacggcaac cacgaagctg ccaaaatt
                                                                       338
      <210> 37
      <211> 375
      <212> DNA
      <213> E. Coli
ctgaatattt aaaaaggaaa acgacatgaa accgaagcac agaatcaaca ttctccaatc
ataaaatatt toogtggago attttattat tgaatataga ggtttaacto oggtaaaaaa
                                                                       120
caaagaagca ttgaatgcag ggaaaaataa tatggccata aaaaacatcg aaagaaactc
                                                                       180
ttttaattta acatgtaaac gcatggttaa tcctcatatc acgggtggag tgttaagaac
                                                                       240
atacataaat ggagtcatgt tttccctttt ccatttatca agttcctgtt gccgttttag
                                                                       300.
tocatotota attgcatatt ttaattttto tgataaatgg cattgagcat cgatttcatt
                                                                       360
taaaacaact gtaca
                                                                       375
      <210> 38
      <211> 446
      <212> DNA
      <213> E. Coli
      <400> 38
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tgactacctt cgtttttttg attaagaatg attttattat cgtaagtaaa attacatgaa
                                                                       120
tatttaaaaa ggaaaacgac atgaaaccga agcacagaat caacattctc caatcataaa
                                                                       180
atatttccgt ggagcatttt attattgaat atagaggttt aactccggta aaaaacaaag
                                                                       240
aagcattgaa tgcagggaaa aataatatgg ccataaaaaa catcgaaaga aactctttta
                                                                       300
atttaacatg taaacgcatg gttaatcctc atatcacggg tggagtgtta agaacataca
                                                                       360
taaatggagt catgttttcc cttttccatt tatcaagttc ctgttgccgt tttagtccat
                                                                       420
ctctaattgc atattttaat ttttct
      <210> 39
      <211> 392
      <212> DNA
      <213> E. Coli
      <220>
      <221> misc_feature
      <222> (1)...(392)
      <223> n = A,T,C or G
     <400> 39
tcaccccggt gccgattttc aggcatcctg atttaactta gcacccqcaa cttaactaca
                                                                        60
ggaaaacaaa gagataaatg totaatootg atgcaaatog agoogatttt ttaatottta
                                                                      120
cggactttta cccgcctggt ttattaattg cactgtnatc cgggcgttcg cccgctttaa
                                                                      180
tcacaatagg ctgtgtagcc tgggcctgtt tctctttcac ccgcgccaga gcggcagcaa
                                                                      240
```

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togcatottt atotttggot goaggttgaa oggotgogot ottatgtogt toaaggogag
cogettttte gegetecaga egageetgge gegettegaa acgegetttg gettetgegg
                                                                         360
                                                                         392
cnegetttte tteetgacga atageegeaa tt
      <210> 40
      <211> 208
      <212> DNA
      <213> E. Coli
taataacgct atctgcggat aaagcagaat aggtggttaa ccccagacat aaaccgagga
                                                                           60
aaataatgtt attgtatttc ataatctatt gttccttagc gacagattgc tgtctgctgg
                                                                         120
ttcagtaagg taccaggaga aacttcagga agcttgtact cgacaataca gtttgagttt
                                                                         180
ttatctttgc cccatgaaac ctgtaatt
                                                                         208
      <210> 41
      <211> 342
      <212> DNA
      <213> E. Coli
      <400> 41
catcolcaat acceptiaaat gcaaccegaa cocceptigt coottigete cattoactta
acgtaatctg aaaagggacg gctggacttg tgctaccggt cgttggaaat tgtctggcac
                                                                          120
tgttttttg gagatctacg gtaaaattaa gcgaatccga tgagactgtg cagccataat cgaggacgcg cccgctaatt ttaataacgc tatctgcgga taaagcagaa taggtggtta
                                                                          180
                                                                          240
accecagaca taaaccgagg aaaataatgt tattgtattt cataatctat tgttccttag
                                                                          300
cgacagattg ctgtctgctg gttcagtaag gtaccaggag aa
                                                                          342
      <210> 42
      <211> 841
      <212> DNA
      <213> E. Coli
      <220>
      <221> misc_feature
      <222> (1) ... (841)
      <223> n = A,T,C or G
      <400> 42
agatttactg ccaatttccg gcagatcgga aagggttaaa ccatattgat ccataagggt
                                                                           60
acquatcacq gctataccqc caggcatqqc ttqaqccatq qcattaaatt ccqcaaattc
                                                                          120
gggcgctgat tetteccaeg eggttatttt ggcacaeace agatecagea aggggttnte
                                                                          180
aggatogttg agcagcagat gatotaccag tincagogco tgggtgtatt gntcottgtt
                                                                          240
ctgaataccc gnnagaaaag gtgccacagc anttagettn tetectgett gcaagatgte
                                                                          300
                                                                          360
tggcaatngc aatcattttt tgcacttant acgatgnaca nongtaaaga aatcgnattt
                                                                          420
tintatgoog toataactit acgtatgtan cactititigo nationaaaa aagaccattn
                                                                          480
gctncaacac gtaaatttna ttgnccccna catttanaac ataaatgntt aaaattttcc
occononnan tittaagnin tinanagaat ngggaattac cigcittina aignactcan
                                                                          540
antititing naataattoo intatonaan cinntition occaanagno nnocaaatin
                                                                          600
eggtttnntn nttnnenngg entttttta ecenanaann tttatteaan neettttttg
                                                                          660
                                                                          720
tagnotatit naagnggnot tintinnati aactiteenn tiggnoaaat titggonnat
ttttatatan aattntctta tntcntaatt tnggnanccc cngatgnaan tttatggngg
                                                                          780
gantecennt ecetntttaa tnnatgntet gggntatttt taaaneetnn attaannnan
                                                                          840
                                                                          841
       <210> 43
       <211> 215
       <212> DNA
       <213> E. Coli
       <400> 43
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aataactttt cgttaggcag ttttgggtgt gagttgcaag aggggagact actgaataac
tcaagtttta taatcgaggg gaaaatggtg atggcgttca tagcaaaacg ccctcaacca
                                                                          120
tamaqqtcqa qqqcqcttam qatqttamam acccqctatc cqttamamam camtqttcam
                                                                          180
ctaaggtcag tgacattgcg ctaaaaaagc gaatt
                                                                          215
      <210> 44
      <211> 395
      <212> DNA
      <213> E. Coli
      <220>
      <221> misc_feature
      <222> (1)...(395)
      <223> n = A, T, C or G
      <400> 44
gcattattca tgagaaatgt gtatcgtaaa tcaactgaaa ttaacgcaac catttgttat
                                                                           60
ttaaggttta attatctgtg tgtgatattt tattgaatgt tttaaatatt gttttattg
                                                                         120
gcattgctat aatattggtt atcatttgct gaatggattc agtcttaatg agtgggtttt
                                                                         180
taagggacag gcatagagta atgatacgta tgcataacca acatetttac teattatgte
                                                                          240
attgaatgtt gaccctatgt gtttatgaag gagaggtatt ttcagttgat ctggattgnt
                                                                         300
aaattcatat aatgcgcctt tgctcatgaa tggatgccag tatgtagtgg gaaattataa
                                                                          360
atattgaaat agtccaacta cttctttatt accaa
                                                                          395
      <210> 45
      <211> 883
      <212> DNA
      <213> E. Coli
      <220>
      <221> misc_feature
      <222> (1)...(883)
      <223> n = A, T, C or G
ataatcaggt aagaaaaggt gcgcggagat taccgtgtgt tgcgatatat tttttagttt
cgcgtggcaa tacatcagtg gcaataaaac gacatatcca gaaaaatata cactaagtga atgatatctt ccgatttatc ttaatcgttt atggataacg gcaaaggget tcgtttttc
                                                                          120
                                                                          180
                                                                          240
ctatacttat tcagcactca caaataaagg aacgccaatg aaaattatac tctgggctgt
attgattatt ttcctgattg ggctactggt ggtgactggc gtatttaaga tgatatttta
                                                                          300
aaattaatta atgtcatcag gtccgaaaat aacgagaata tttcagtctc tcatcctgtt
                                                                          360
gegeteetgt catgtgcatt getteatata atcactggeg caaggagege egeaggegna
                                                                          420
gnntgenegn egneceacet naccecatge egaactteag aantgaaaac neentaacne
                                                                          480
cgatngtcgg cgggngcctc cccatgcnan agtangggaa ntgccangcg ncnnattaaa
                                                                          540
                                                                          600
cqaaaggctn attncaaaga ctgggccttn cntttatctg atgtttgtcg gagaacgctc
                                                                          660
tcctgagnan gacaaatncc gccgggagcg gatttgaacn ttgcgaagca accgncccna
agggngnngt entgachece nnetetanet nnengeette ttttgettna angneeteet
                                                                          720
                                                                          780
anchgatgge ctttttngcc ntctaccaaa cnntttggtt aatgcttnta aaancettte
cannithcaa teengtinth eccateenin tintgaaagn ntheetheen tgtheantht
                                                                          840
anntnngggg gnngngngcc ggcggncccc cccccccc ccc
                                                                          883
      <210> 46
      <211> 1024
      <212> DNA
      <213> E. Coli
      <220>
      <221> misc_feature
      <222> (1) ... (1024)
      <223> n = A, T, C or G
```

```
<400> 46
gtttatggat aacggcaaag ggcttcgttt tttcctatac ttattcagca ctcacaaata
                                                                        60
aaggaacgcc aatgaaaatt atactetggg etgtattgat tatttteetg attgggetae
                                                                       120
tggtggtgac tggcgtattt aagatgatat tttaaaatta attaatgtca tcaggtccga
                                                                       180
aaataacgag aatatttcag teteteatee tgttgegete etgteatgtg cattgettea
                                                                       240
tataatcact ggcgcaagga gcgcgcagag tnctccnant nnnnntnntt ntntnnctnn
                                                                       300
ncetteacna thenneenen nanthnatag nneacennth ttnntennnn gneeneetee
                                                                       360
nnncnnnnn ncatnnnatc ccactnnntt thetecannn nnncnnnntn cancenacaa
                                                                       420
anthonacch annthacctt atachnanne nanchnnnn nnecacteth netegnnete
                                                                       480
ccenttenae nnecannnnn canenntenn etnnnnecet nnentaattn ttetnnetan
                                                                       540
ntectancen ennaennnee eanenateen nnnataeant enattnntnn enntenentn
                                                                       600
encennttee nnetnnnene thecheathe commannan canninecee neetheetha
                                                                       660
concnence conceated nnnconnent connantnga caannnnaat enennnnen
                                                                       720
nnnnnnnnn tnnnenecen genenneent neenteaene tnnnenneta nannnnntae
                                                                       780
nntnacennt cetnneacne thecetnnng antecnaena ntnnnnnane nanaacnetn
                                                                       840
thnnnccata atoccacaco achecentre amentnini mententece tientatene
                                                                       900
agetnnnnnt netntnnnne tneeneeenn ennaetnenn nnaecenenn eccanteagt
                                                                       960
ccacenteen ennennnntn nnnenanean etnneaenen enantaacet nntnneaeet
                                                                      1020
tece
                                                                      1024
      <210> 47
      <211> 236
     ~<212> DNA
      <213> E. Coli
      <400> 47
atatacacta agtgaatgat atcttccgat ttatcttaat cgtttatgga taacggcaaa
                                                                        60
gggcttcgtt ttttcctata cttattcagc actcacaaat aaaggaacgc caatgaaaat
                                                                       120
tatactctgg gctgtattga ttattttcct gattgggcta ctggtggtga ctggcgtatt
                                                                       180
taagatgata ttttaaaatt aattaatgtc atcaggtccg aaaataacga gaatat
                                                                       236
      <210> 48
      <211> 418
      <212> DNA
      <213> E. Coli
      <220>
      <221> misc_feature .
      <222> (1) ... (418)
      <223> n = A, T, C or G
      <400> 48
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ataaaacgac atatccagaa aaatatacac taagtgaatg atatcttccg attnatctta
                                                                       120
ntegittatg gataacggca aagggetteg tittiteeta taettattea geacteacaa
                                                                       180
ataaaggaac gccaatgaaa attatactct gggctgtatt gattattttc ctgattgggc
                                                                       240
tactggtggt gactggcgta tttaagatga tattttaaaa ttaattaatg tcatcaggtc
                                                                       300
cgaaaataac gagaatattt cagtototoa tootgttgcg otootgtcat gtgcattgct
                                                                       360
toatataatc actggcgcaa ggagcgcgca nggggcggcc aatcgccgcc ggcccctg
                                                                       418
      <211> 550
      <212> DNA
      <213> E. Coli
      <400> 49
ctgctagtta cagggaacac taatgacaga cagctaaaag ccctgtttaa ttacgtatta
caaacagggg atgcccageg ttttcgtgca tttattggtg agatagcgga acgcgcacca
                                                                      120
caagaaaagg agaaactgat gaccattgct gacagattac gtgaagaagg cgcaatgcag
                                                                      180
ggcaaacacg aagaagccct gcgtattgct caggagatgc tggatagagg tttagacaga
                                                                      240
gagttagtta tgatggtgac ccgactttca ccagacgatc ttatcgcgca aagccactaa
                                                                      300
```

```
tcctgtaaca ccgggagtta actggcggat gtttgctgta aaccacatca gcgaacgaca
                                                                          360
tecgecageg cetettetaa ategtaceag egaaaegeaa aaceegette ttecageegt
                                                                          420
ttaggcagcg cgcgttgtcc acctaatacc agtactgaag attcgcccat taacagtcga
                                                                          480
atggcggtcg cggggacgcg caaaatggcc gggcgatgca gcgcatgacc gagcgcatgg
                                                                          540
gcaaattgtt
                                                                          550
      <210> 50
      <211> 99
      <212> DNA
      <213> E. Coli
      <400> 50
ttggcatctc ggtgttgccg atcttcatga tatccagccc gccggaaact tcttcccaaa
                                                                           60
cggttttgct gttatccatt gagtcacgga actgecct
                                                                           99
      <210> 51
      <211> 259
      <212> DNA
      <213> E. Coli
      <220>
      <221> misc_feature
      <222> (1) ... (259)
      <223> n = A, T, C or G
      <400> 51
ccgtgccgag atgatectgt naccateate cgttgtgaag tagtgattea cgaetteaag
                                                                           60
gegettttea aaagggtatt ttggetttga catattaggg getatteeat tteategnee
                                                                          120
aacaaaatgg gtgcagtaca tactcnttgg aaatcaacac aggaggctgg gaatgccgca
                                                                          180
gaaatataga ttactttctt taatagtgat ntgtttcacg cttttatttt tnaaanaagt
                                                                          240
tnggcttact tcccgggnn
                                                                          259
      <210> 52
      <211> 877
      <212> DNA
      <213> E. Coli
      <220>
      <221> misc_feature
      <222> (1)...(877)
      \langle 223 \rangle n = A,T,C or G
cagcagagcg cggccttctt cgtcagattt cgcagtagtg gtaatggtaa tatccaaacc
                                                                           60
acgaacgcgg tcgactttat cgtagtcgat ttctgggaag atgatctgct cacggacacc
                                                                          120
catgctgtag ttaccacgac cgtcgaaaga cttagcggac aggccacgga agtcacggat
                                                                          180
acgaggtaca gcaatagtga tcaggcgctc aaagaactcc cacatgcgtt cgccacqcag
                                                                          240
agttacttta cagccgatcg gatagccctg acggattttg aagcctgcaa cagatttgcg tgctttggtg atcagcggtt tttgaccgga gattgctgcc aggtctgctg ctgcgttatc
                                                                          300
                                                                          360
cagcagtttt ttgtcagcga tcgcttcacc aacacccatg ttcagggtga tcttctcgac
                                                                          420
ccgagggact tgcatgacag aattgtagtt aaactcagtc atgagttttt taactacttc
                                                                          480
gtctttgtag taatcatgca gtttcgccat cgtactactc catgtcggtg aacgctctcc
                                                                          540
tgagtaggac aaatccgccg ggagcggatt tgaacgttgc gaagcaacgg cccggagggt
                                                                          600
ggcgggcagg acgcccgcca taaactgcca ggcatcaaat taagcagaag gccatcctga
                                                                          660
cggatggcct ttttgcgttt ctacaaactc ttttggttat ttttctaaat cattcaaata
                                                                          720
tgtatccgnt catcccatcc tatcgatgat aagctgtcaa acatgagaat ttaatcaatc
                                                                          780
taaagtttta tggngttaaa cttgggctgg cagnttncca atggcttaat cagtngaggg
                                                                          840
ccctatntta acgaactngg ctantttngg tcaatcn
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      <210> 53
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WO 00/44906				PC	T/US00/02200
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tottcacaaa aataataata gattttatta cgcgatcgat tatttattto ctgaaaacaa
                                                                          300
ataaaaaaat ccccgccaaa tggcagggat cttagattct gtgcttttaa gcagagatt
                                                                          359
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      <211> 700
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caccaaaacg tgccgagatg atcctgtaac catcatcagt tgtgaagtag tgattcacga
                                                                          120
cttcaaggcg cttttcaaaa gggtattttg gctttgacat attaggggct attccatttc
                                                                          180
atcgtccaac aaaatgggtg cagtacatac tcgttggaaa tcaacacagg aggctgggaa
                                                                          240
tgccgcagaa atatagatta ctttctttaa tagtgatttg tttcacgctt ttattttca
                                                                          300
cctggatgat aagagattca ctgtgtgaat tgcatattaa acaggagagt tatgagctgg
                                                                          360
cggcgttttt agcctgcaaa ttgaaagagt aagagtcttc ggcgggaaat tattcccgcc
                                                                          420
ttacttacgg cgttgcgcat tctcattgca cccaaattta ttcttcacaa aaataataat
                                                                          480
agattttatt acgcgatcga ttatttattt cctgaaaaca aataanaaaa tccccgccaa
                                                                          540
atggcaggga tettagatte tgtgetttta agcagagatt acaggetggt tacgttacca
                                                                          600
getgeeggge etttaaegee getttegatg gtgaaggaca etttetgace ttegteeaga gattgtaaec ateggtetgg atageenaga aatgteeaae
                                                                          660
                                                                          700
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      <211> 631
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                                                                           60
                                                                          120
caccacgggg gctaatcttg actctagacc actcaagaat agccgcgaaa cgttgtcatt
                                                                          180
acaacacagg cggctatatg acgttcgcag agctgggcat ggccttctgg catgatttag
cggctccggt cattgctggc attcttgcca gtatgatcgt gaactggctg aacaagcgga
                                                                          240
agtaacgtgt catgcgggcg tcaggctgcc gtaatggcaa tttgcgcccg gaccaggccg
                                                                          300
cagggggaa actotgoggo ctttttcqtt cttactgcgg gtaaggcacc cagtcgccgc
                                                                          360
cgttcaggcg aacgtacggt ttatcctggt attgaataac tactgcattt gagttctcgg
                                                                          420
agaccggtgc tgtttgtggc aacccactgg tgagtttttt ccagtcaaca ttgtcttcgg
                                                                          480
                                                                          540
tgaaaatctt gccatcgaga acgcgaacca ccagatcgga gatagccagg aagctgctcg
gttgttcgat gacaatcggt gccccctgat gcggtgcctt catgccgaag aatttcaccc
                                                                          600
caacggggac gtcngtgata gaccgggcta g
                                                                          631
      <210> 60
      <211> 648
      <212> DNA
      <213> E. Coli
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      <400> 60
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atggagagaa tcataaacgt ggtgaatgat gattgttagc aaggaaaact gtcaaaaatc
                                                                        120
ttcaaaaaat ttgagggata aggccggaat ggctccggcc agagggaagt taaccgcgaa
                                                                        180
gctgttgctg cttgagggtc gttttaacca gacgccaggc gctccatacg ccaaaaccgc
                                                                        240
gtctggccca gcggaccagc atattaggat ggcgaatcgt ccagatcgcc atcacgctac
                                                                        300
tgccaaccag cgcccaggag cgcagactta gcagcatatt ccancgacga tcgtaagcgc
                                                                        360
ctgttgtctc cagccattca cgacgactgg cggaagggnc cgcgnctgac caacttgnct
                                                                        420
tttagnotga tnoanattan attnataaac goagnannon ggtntgatta atontatttn
                                                                        480
getetngtet ggtagttage nneggnnngt etentinina ecennitenn titannitae
                                                                        540
natnngtaan ttatntttnt nngtotnant tntanttgng tactntaagt ntatnognnn
                                                                        600
atnothnoan nonneagene ntnttttta aatnotttnt nannenne
                                                                        648
      <210> 61
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      <212> DNA
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aaacggaggc aaataatgct gggtaatatg aatgttttta tggccgtact gggaataatt
                                                                       120
ttattttctg gttttctggc cgcgtatttc agccacaaat gggatgacta atgaacggag
                                                                       180
ataatccctc acctaaccgg ccccttgtta cagttgtgta caaggggcct gatttttatg
                                                                       240
acggcgaaaa aaaaccgcca gtaaaccggc ggtgaatgct tgcatggata gatttgtgtt
                                                                       300
ttgcttttac gctaacaggc attttcctgc actgataacg aatcgttgac acagtagcat
                                                                       360
cagttttctc aatgaatgtt aaacggagct taaactcggt taatcacatt ttgttcgtca
                                                                       420
ataaacatgc agcgatttct tccggtttgc ttaccctcat acattgcccg gtccgctctt
                                                                       480
ccaatgacca catccagagg ctcttcagga aatgcgcgac tcacacctgc tgtcacggta
                                                                       540
atgttgatat gcccttcaga atgtgtgatg gcatggttat cgactaactg gcaaattctg
                                                                       600
acacctgcac gacatgcttc ttcatcatta gccgctttga caataatgat aaattcttcg
                                                                       660
cccccgtagc gataaaccgt ttcgtaatna cgcgtccaac tgggntaagt aaagttgcca
                                                                       720
gggtgccgta atcttac
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                                                                        60
aaaaccgata atctgaaaga acccaagtat ttcagtataa gcattgaatg ccgaccagta
                                                                       120
aactotttog gattoaccca gaaagtgaan ccaaaatgat aatogtatac ataagtottt
                                                                       180
cgagtggctc gttagcaaaa agtttcaaca atggagtaaa tacatccaac atatcaataa
                                                                       240
ctctcaactg taaggggatt gaaatggtaa ccccagetet tegettgagg ggtatageeg
                                                                       300
agaccaccga agccccggag gtggtgaaat aaaaccgggc acaacacgaa agggcgcatt
                                                                       360
tccgatatcc ataaaagaag tcgggtcttt gtctggtaaa attaaattgg tgggaagtgc
                                                                       420
gcctccgggt tgtaaatacc gactttgctg ggtgtagcct ggcggcatca agtttttttc
                                                                       480
tggaagttcg ctgatgtccg cccttttaa agggaatttt ggtgatgccg gtgaatgccg
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cttaaccccc cgtgggccca gttaaaagtc atggtaagnc ctaatnggtt tggggtggga
                                                                       600
aaagccnact gnnaattggt tacctggttt gcaagtance ctggaagg
                                                                       648
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acaacaatga ttataatagc aaaaataaat attatcatct ttgatagatt acttgagata
                                                                       120
gccagcatct tgtaaagcct ttatcgtttt tttatgctct ggattaatat aatcactaca
                                                                       180
tctatctgag caatctgttg ttgatggaca tgtcaaccca tggtcattta cagccaa
                                                                       237
      <210> 64
      <211> 427
      <212> DNA
      <213> E. Coli
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                                                                        60
aatcatgcca ttagtcattg ttgctatcgg tgtaatcttg ttgttgctcc tgatgatccg
                                                                       120
cttcaaaatg aacggettca tegetetegt cetegtggeg ettgetgttg gattaatgea
                                                                       180
aggaatgccg ctggataaag ttattggctc catcaaagcc ggtgtcggcg ggacgctcgg
                                                                       240
tagccttgcc ctgatcatgg gttttggcgc aatgctgggc aaaatgctgg cagactgcgg
                                                                       300
tggcgcacaa cgtatcgcca ccacgctgat tgccaaattt ggtaaaaaac acatccagtg
                                                                       360
ggcggtggta ctgaccggtt ttaccgttgg ttttgccctg ttctatgaag tgggctttgt
                                                                       420
gctgatg
                                                                       427
      <210> 65
      <211> 261
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aattaatgca attatcgaaa attcaaaaaa tatccaaaaa tngtatactt tattccagaa
                                                                       120
gagttcaata taatgtttgt cttcaatttt tcttacttca gggtaatata gattgctcat
                                                                       180
tacattgtga getteatett tatttaattt tetgttgaet eeagetetee gtgataaegg
                                                                       240
ttttataatt agatgcttat c
                                                                       261
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      <211> 98
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ctttacgtac ttctgcgttg atagtaaaca tttctttc
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                                                                           60
                                                                          120
cagetttage ttgcatgtte atgactttgt egtgatecag etegatagee ageggegett
                                                                          180
ctttgccacc gragatgatt gccgggaact tgttagcggc acgcaggcgg cggctcgcac
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cettacectg ctetttacgt
                                                                          260
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      <211> 95
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tatattacge egcaaaatce ttacaataaa caggg
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agcggggagg ggaggtaaag tgaaaaaata aaaagcggat aatcttaata agcaggccgg
                                                                          120
                                                                          174
acagcatcgc catccggcac tgatacgagg tttatttcag ctcatcaacc atcg
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      <211> 138
      <212> DNA
      <213> E. Coli
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gtagtaatgc aaaaaaatgg agacttaagt tgaatgaacg ggagtaaagc gaaaagacta
                                                                          120
                                                                          138
tagagtgaag gagaaatt
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      <211> 191
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      <213> E. Coli
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gtttttggag agaagaatga ggaagatgcg tcgagccaca gaaacgttag ctttacatat
                                                                          120
                                                                          180
agcggaggtg atgtgaattt aatttacaat agaaataatt tacatatcaa acagttagat
gctttttgtc g
                                                                          191
      <210> 72
      <211> 244
      <212> DNA
      <213> E. Coli
ggccatttat acaggaaaag cotatgtoag aacgtaaaaa ctcaaaatca cgccgtaatt
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atorogitaa argitocigo coaaactgoa cocaagagto agaacacagt tittoaagag
                                                                          120
tacaaaaagg tgcccttttg atctgccctc attgcaacaa agtattccag acaaatctta
                                                                          180
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aagctgtagc ctgattgatt ttattagtaa caagtatttt ttatatttta ataatatatt
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taaa
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<211> 327

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<210> 74 <211> 150 <212> DNA <213> E. Coli					
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<210> 75 <211> 330 <212> DNA <213> E. Coli					
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<210> 76 <211> 194 <212> DNA <213> E. Coli					
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<210> 77 <211> 188 <212> DNA <213> E. Coli					
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<210> 8 <211> 2 <212> 0 <213> 0	259					
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<210> 8 <211> 7 <212> 1 <213> 8	73 DNA					
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ctggcaccga cagcgtccac attgccttct ggcgtagccc	ggatgccttt	atggctgaac	actggatgga	aatcqcqctq	480 540
gtcgattact gtttcaaagt ttactcaata tgctgttgaa agttaa	aagactggca	gataaatccg	aaatcaacgc	gtatggcgta tttgcaggcg	600 660 666
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aaagacacta acgctacggc	gcagggttcg	gtcgcggaaa	gtaacgctac	cgggaatccc	180
gtcaacctgc ttgatggcaa					240
ggtaagctgg gaacgcaggc					300
gcagtcatcg tcatcatggg	cgatgatccg	aaagaagatc	tggcggtgct	ggcgaagcgt	360
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gagctgaaag gtcacaaaat	gcagcagtta	gacagtatta	tctccgcgaa	aggccagacg	480
gcgtactctt ccgttattct					540
ctgcccgctg acgatcagca	aaaagcgcag	accaccgcag	aaaacatcat	taatacgctg	600
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ctggaaaccg gtgcttctgt					240
atttatgaac cgttccagat					300
tttattctgg tagagaagtt					360
atcgaaaccg gtcatccgaa aagcttgatt acatcaagcg					420 480
gtctcaaaag agctgacgat					540
ctgccggtca cctactcaaa	cotogaacco	aggatttcg	ttcagacctt	ctcacaccat	600
aatggtgggg aagcgaccag					660
ggaattcgtc tttccgagcg					720
gtgccgattg cgcaggatca					780
acctggattg ttcctccggg	acaatacttc	atgatgggcg	acaaccgcga	caacagcgcg	840
gacagccgtt actggggctt	tgtgccggaa	gcgaatctgg	tcggtcgggc	aacggctatc	900
teentenent teentanen					0.00

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960

975

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ggcggcatcc attaa

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cggctgcaat ttgcgctgga gcagttgctg catacqcqag catcctcc ttttatgctg 180
gcgaaggccc cggaagagtc tgagtatctg aatcttattg ccaatgccgc gcgtacgcta 240
caaagcgatg caggccaact ggtggcggt cactatgagg tttccggcca ctccatccgc 300
ttacgtcacg cagtgagtgc agatgataat tttgcgactt taacgcaagt tgtcgctgcc 360
gactgggtag aagcggagca actctttggc tgcctgcgcc agtttaatgg cgacattacc 420
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tggatgaget tegataagea agaaggegaa tggeegactg gtetgegett aagtegeatt

```
ctgcagcctg gtctggtgca tcaggcaaat ggcggtattc tcattatctc tttgcgtaca
ctgctggcgc aacctctgct gtggatgcgg ctgaaaaata tcgttaaccg cgagcgtttt
                                                                        540
gactgggttg cgtttgatga gtcgcgccct ctccccgtct ctgtgccttc gatgccattg
                                                                        600
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Glu Val Pro Leu Ser Glu Met Phe Gly Tyr Ala Thr Gln Leu Arg Ser 660 665 670

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 Ile
 Leu
 Met
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 Asp
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115
120
125
Thr Leu Acc Nie Glu Ile Ala Lys Thr Leu Asn Ala Glu Ile Val Phe Val Met Ser Gln Gly Thr Asp Thr 130 135 140 Pro Glu Gln Leu Lys Glu Arg Ile Glu Leu Thr Arg Asn Ser Phe Gly 145 150 155 160 Gly Ala Lys Asn Thr Asn Ile Thr Gly Val Ile Val Asn Lys Leu Asn 165 170 175 Ala Pro Val Asp Glu Gln Gly Arg Thr Arg Pro Asp Leu Ser Glu Ile 180 185 190 Phe Asp Asp Ser Ser Lys Ala Lys Val Asn Asn Val Asp Pro Ala Lys 195 200 205 Leu Gln Glu Ser Ser Pro Leu Pro Val Leu Gly Ala Val Pro Trp Ser 210 225 220 Phe Asp Leu Ile Ala Thr Arg Ala Ile Asp Met Ala Arg His Leu Asn 225 230 235 240 Ala Thr Ile Ile Asn Glu Gly Asp Ile Asn Thr Arg Arg Val Lys Ser 245 250 255 Val Thr Phe Cys Ala Arg Ser Ile Pro His Met Leu Glu His Phe Arg 260 265 270 Ala Gly Ser Leu Leu Val Thr Ser Ala Asp Arg Pro Asp Val Leu Val 275 280 285 Ala Ala Cys Leu Ala Ala Met Asn Gly Val Glu Ile Gly Ala Leu Leu 290 295 300 Leu Thr Gly Gly Tyr Glu Met Asp Ala Arg Ile Ser Lys Leu Cys Glu 305 310 315 320 Arg Ala Phe Ala Thr Gly Leu Pro Val Phe Met Val Asn Thr Asn Thr 325 330 335 335 Trp Gln Thr Ser Leu Ser Leu Gln Ser Phe Asn Leu Glu Val Pro Val 340 345 350 Asp Asp His Glu Arg Ile Glu Lys Val Gln Glu Tyr Val Ala Asn Tyr 355 360 365 Ile Asn Ala Asp Trp Ile Glu Ser Leu Thr Ala Thr Ser Glu Arg Ser 370 375 380 Arg Arg Leu Ser Pro Pro Ala Phe Arg Tyr Gln Leu Thr Glu Leu Ala 385 390 395 400

430

Arg Lys Ala Gly Lys Arg Ile Val Leu Pro Glu Gly Asp Glu Pro Arg 405 410 415 Thr Val Lys Ala Ala Ala Ile Cys Ala Glu Arg Gly Ile Ala Thr Cys 425

Val Leu Leu Gly Asn Pro Ala Glu Ile Asn Arg Val Ala Ala Ser Gln 435 440 445 Val Glu Leu Gly Ala Gly Ile Glu Ile Val Asp Pro Glu Val Val 450 455 460 450 455 460 Arg Glu Ser Tyr Val Gly Arg Leu Val Glu Leu Arg Lys Asn Lys Gly
465 470 475 Met Thr Glu Thr Val Ala Arg Glu Gln Leu Glu Asp Asn Val Val Leu 485 490 495 Gly Thr Leu Met Leu Glu Gln Asp Glu Val Asp Gly Leu Val Ser Gly 500 505 510 Ala Val His Thr Thr Ala Asn Thr Ile Arg Pro Pro Leu Gln Leu Ile 515 520 525 Lys Thr Ala Pro Gly Ser Ser Leu Val Ser Ser Val Phe Phe Met Leu 530 535 540 Leu Pro Glu Gln Val Tyr Val Tyr Gly Asp Cys Ala Ile Asn Pro Asp 545 550 555 560 Pro Thr Ala Glu Gln Leu Ala Glu Ile Ala Ile Gln Ser Ala Asp Ser 565 570 575 Ala Ala Ala Phe Gly Ile Glu Pro Arg Val Ala Met Leu Ser Tyr Ser 580 585 590 Thr Gly Thr Ser Gly Ala Gly Ser Asp Val Glu Lys Val Arg Glu Ala 595 600 605 Thr Arg Leu Ala Gln Glu Lys Arg Pro Asp Leu Met Ile Asp Gly Pro 610 615 620 Leu Gin Tyr Asp Ala Ala Val Met Ala Asp Val Ala Lys Ser Lys Ala 625 630 635 640 Pro Asn Ser Pro Val Ala Gly Arg Ala Thr Val Phe Ile Phe Pro Asp 645 650 655 Leu Asn Thr Gly Asn Thr Thr Tyr Lys Ala Val Gln Arg Ser Ala Asp
660 665 670 Leu Ile Ser Ile Gly Pro Met Leu Gln Gly Met Arg Lys Pro Val Asn 675 680 685 Asp Leu Ser Arg Gly Ala Leu Val Asp Asp Ile Val Tyr Thr Ile Ala 690 695 700 Leu Thr Ala Ile Gln Ser Ala Gln Gln Gln 710

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 Ile Ile Asp Asn Val Ser Ile Leu Asp Leu Ile Asn Gly Gly Glu Ile 35
 40

 Ser Gly Pro Ile Val Ile Lys Gly Arg Tyr Ile Ala Gly Val Gly Ala 50
 55

 Glu Tyr Thr Asp Ala Pro Ala Leu Gln Arg Ile Asp Ala Arg Gly Ala 65
 70

 Thr Ala Val Pro Gly Phe Ile Asp Ala His Leu His Ile Glu Ser Ser 90
 95

 Met Met Thr Pro Val Thr Phe Glu Thr Ala Thr Leu Pro Arg Gly Leu 100
 100

 Thr Thr Val Ile Cys Asp Pro His Glu Ile Val Asn Val Met Gly Glu 115
 120

 Ala Gly Phe Ala Trp Phe Ala Arg Cys Ala Glu Gln Ala Arg Gln Asn

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130
Gln Tyr Leu Gln Val Scr Scr Cys Val Pro Ala Leu Glu Gly Cys Asp
145 150 155 160
Val Asn Gly Ala Ser Phe Thr Leu Glu Gln Met Leu Ala Trp Arg Asp
165 170 175
                                                                   175
His Pro Gln Val Thr Gly Leu Ala Glu Met Met Asp Tyr Pro Gly Val
180 185 190
Ile Ser Gly Gln Asn Ala Leu Leu Asp Lys Leu Asp Ala Phe Arg His
Leu Thr Leu Asp Gly His Cys Pro Gly Leu Gly Gly Lys Glu Leu Asn
210 215 220
Ala Tyr Ile Thr Ala Gly Ile Glu Asn Cys His Glu Ser Tyr Gln Leu
225 230 235 240
Glu Glu Gly Arg Arg Lys Leu Gln Leu Gly Met Ser Leu Met Ile Arg
245 250 255
Glu Gly Ser Ala Ala Arg Asn Leu Asn Ala Leu Ala Pro Leu Ile Asn
260 265 270
Glu Phe Asn Ser Pro Gln Cys Met Leu Cys Thr Asp Asp Asp Asn Pro
275 280 285
Trp Glu Ile Ala His Glu Gly His Ile Asp Ala Leu Ile Arg Arg Leu
290 295 300
Ile Glu Gln His Asn Val Pro Leu His Val Ala Tyr Arg Val Ala Ser
305 310 315 320
Trp Ser Thr Ala Arg His Phe Gly Leu Asn His Leu Gly Leu Leu Ala 325 330 335
Pro Gly Lys Gln Ala Asp Ile Val Leu Leu Ser Asp Ala Arg Lys Val 340 345 350
Thr Val Gln Gln Val Leu Val Lys Gly Glu Pro Ile Asp Ala Gln Thr 355 360 365
Leu Gln Ala Glu Glu Ser Ala Arg Leu Ala Gln Ser Ala Pro Pro Tyr
370 375 380
Gly Asn Thr Ile Ala Arg Gln Pro Val Ser Ala Ser Asp Phe Ala Leu 385 390 395 400 Gln Phe Thr Pro Gly Lys Arg Tyr Arg Val Ile Asp Val Ile His Asn 405 410 415
Glu Leu Ile Thr His Ser His Ser Ser Val Tyr Ser Glu Asn Gly Phe
420 425 430
Asp Arg Asp Asp Val Ser Phe Ile Ala Val Leu Glu Arg Tyr Gly Gln
435 440 445
Arg Leu Ala Pro Ala Cys Gly Leu Leu Gly Gly Phe Gly Leu Asn Glu
450 455 460
Gly Ala Leu Ala Ala Thr Val Ser His Asp Ser His Asn Ile Val 465 470 475 480
Ile Gly Arg Ser Ala Glu Glu Met Ala Leu Ala Val Asn Gln Val Ile
485 490 495
Gln Asp Gly Gly Leu Cys Val Val Arg Asn Gly Gln Val Gln Ser 505 510
His Leu Pro Leu Pro Ile Ala Gly Leu Met Ser Thr Asp Thr Ala Gln 515 520 525
Ser Leu Ala Glu Gln Ile Asp Ala Leu Lys Ala Ala Ala Arg Glu Cys
530 535 540
Gly Pro Leu Pro Asp Glu Pro Phe Ile Gln Met Ala Phe Leu Ser Leu
545 550 560
Pro Val Ile Pro Ala Leu Lys Leu Thr Ser Gln Gly Leu Phe Asp Gly
565 570 575
Glu Lys Phe Ala Phe Thr Thr Leu Glu Val Thr Glu
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<210> 255 <211> 408 <212> PRT <213> E. Coli

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145 150 155 160 Gly Gly Ser Ala Thr Asn Asp Gly Gly Ala Gly Met Val Gln Ala Leu 165 170 175 Gly Ala Lys Leu Cys Asp Ala Asn Gly Asn Glu Ile Gly Phe Gly Gly
. 180 185 190 Gly Ser Leu Asn Thr Leu Asn Asp Ile Asp Ile Ser Gly Leu Asp Pro 195 200 205 Arg Leu Lys Asp Cys Val Ile Arg Val Ala Cys Asp Val Thr Asn Pro 210 215 220 Leu Val Gly Asp Asn Gly Ala Ser Arg Ile Phe Gly Pro Gln Lys Gly 225 230 235 240 Ala Ser Glu Ala Met Ile Val Glu Leu Asp Asn Asn Leu Ser His Tyr 245 250 255 Ala Glu Val Ile Lys Lys Ala Leu His Val Asp Val Lys Asp Val Pro 260 265 270 Gly Ala Gly Ala Ala Gly Gly Met Gly Ala Ala Leu Met Ala Phe Leu 275 280 285 Gly Ala Glu Leu Lys Ser Gly Ile Glu Ile Val Thr Thr Ala Leu Asn 290 295 300 Leu Glu Glu His Ile His Asp Cys Thr Leu Val Ile Thr Gly Glu Gly 305 310 315 320

Arg Ile Asp Ser Gln Ser Ile His Gly Lys Val Pro Ile Gly Val Ala 325 330 335 Asn Val Ala Lys Lys Tyr His Lys Pro Val Ile Gly Ile Ala Gly Ser 340 345 350 Leu Thr Asp Asp Val Gly Val Val His Gln His Gly Ile Asp Ala Val 355 360 365 Phe Ser Val Leu Thr Ser Ile Gly Thr Leu Asp Glu Ala Phe Arg Gly 370 375 380 Ala Tyr Asp Asn Ile Cys Arg Ala Ser Arg Asn Ile Ala Ala Thr Leu 385 390 395 400 Ala Ile Gly Met Arg Asn Ala Gly

<210> 256 <211> 299 <212> PRT

<213> E. Coli

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35 40 45 40 35 Ala Glu Thr Ala Ser Thr Ala Lys Ala Ile Ala Glu Gln Cys Asp Val 50 60 Ile Ile Thr Met Leu Pro Asn Ser Pro His Val Lys Glu Val Ala Leu 65 70 75 80 Gly Glu Asn Gly Ile Ile Glu Gly Ala Lys Pro Gly Thr Val Leu Ile 85 90 95 Asp Met Ser Ser Ile Ala Pro Leu Ala Ser Arg Glu Ile Ser Glu Ala 100 105 110 Leu Lys Ala Lys Gly Ile Asp Met Leu Asp Ala Pro Val Ser Gly Gly 115 120 125 Glu Pro Lys Ala Ile Asp Gly Thr Leu Ser Val Met Val Gly Gly Asp 130 135 140 Lys Ala Ile Phe Asp Lys Tyr Tyr Asp Leu Met Lys Ala Met Ala Gly 145 150 150 160 Ser Val Val His Thr Gly Glu Ile Gly Ala Gly Asn Val Thr Lys Leu 165 170 175 Ala Asn Gln Val Ile Val Ala Leu Asn Ile Ala Ala Met Ser Glu Ala 180 185 190 Leu Thr Leu Ala Thr Lys Ala Gly Val Asn Pro Asp Leu Val Tyr Gln 195 200 205 Ala Ile Arg Gly Gly Leu Ala Gly Ser Thr Val Leu Asp Ala Lys Ala 210 215 220 Pro Met Val Met Asp Arg Asn Phe Lys Pro Gly Phe Arg Ile Asp Leu 225 230 235 240 His Ile Lys Asp Leu Ala Asn Ala Leu Asp Thr Ser His Gly Val Gly 245 250 255 Ala Gln Leu Pro Leu Thr Ala Ala Val Met Glu Met Met Gin Ala Leu 260 255 270 Arg Ala Asp Gly Leu Gly Thr Ala Asp His Ser Ala Leu Ala Cys Tyr 275 280 285 Tyr Glu Lys Leu Ala Lys Val Glu Val Thr Arg 295 290

<210> 257 <211> 256 <212> PRT <213> E. Coli

<400> 257

<210> 258 <211> 444 <212> PRT <213> E. Coli

<400> 258

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165 170 175 Trp Glu His Val Phe Thr Val Met Gly Val Ile Gly Phe Val Leu Thr 180 185 190 Ala Leu Trp Ile Lys Leu Ile His Asn Pro Thr Asp His Pro Arg Met 195 200 205 Ser Ala Glu Glu Leu Lys Phe Ile Ser Glu Asn Gly Ala Val Val Asp 210 215 220 Met Asp His Lys Lys Pro Gly Ser Ala Ala Ala Ser Gly Pro Lys Leu 225 230 235 240 His Tyr Ile Lys Gln Leu Leu Ser Asn Arg Met Met Leu Gly Val Phe 250

> <210> 259 <211> 511 <212> PRT <213> E. Coli

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Arg Glu Lys Ser Leu Ser Ala Ser Gln Lys Leu Trp Leu Glu Leu Pro 245 250 255 Gly Asn Arg Pro Gln His Ala Ala Gly Thr Pro Val Leu Thr Leu Glu 260 265 270 Asn Leu Thr Gly Glu Gly Phe Arg Asn Val Ser Leu Thr Leu Asn Ala
275
280
285 Gly Glu Ile Leu Gly Leu Ala Gly Leu Val Gly Ala Gly Arg Thr Glu 290 295 300 Leu Ala Glu Thr Leu Tyr Gly Leu Arg Thr Leu Arg Gly Gly Arg Ile 305 310 315 320 Met Leu Asn Gly Lys Glu Ile Asn Lys Leu Ser Thr Gly Glu Arg Leu 325 330 335 Leu Arg Gly Leu Val Tyr Leu Pro Glu Asp Arg Gln Ser Ser Gly Leu 340 345 350 Asn Leu Asp Ala Ser Leu Ala Trp Asn Val Cys Ala Leu Thr His Asn 355 360 365 Leu Arg Gly Phe Trp Ala Lys Thr Ala Lys Asp Asn Ala Thr Leu Glu 370 380 Arg Tyr Arg Arg Ala Leu Asn Ile Lys Phe Asn Gln Pro Glu Gln Ala 385 390 395 400 Ala Arg Thr Leu Ser Gly Gly Asn Gln Gln Lys Ile Leu Ile Ala Lys 405 410 415 Cys Leu Glu Ala Ser Pro Gln Val Leu Ile Val Asp Glu Pro Thr Arg
420 425 430 Gly Val Asp Val Ser Ala Arg Asn Asp Ile Tyr Gln Leu Leu Arg Ser 435 440 445 Ile Ala Ala Gln Asn Val Ala Val Leu Leu Ile Ser Ser Asp Leu Glu
450 455 460 Glu Ile Glu Leu Met Ala Asp Arg Val Tyr Val Met His Gln Gly Glu 465 470 475 480 Ile Thr His Ser Ala Leu Thr Glu Arg Asp Ile Asn Val Glu Thr Ile 485 490 495 Met Arg Val Ala Phe Gly Asp Ser Gln Arg Gln Glu Ala Ser Cys 500 505

<210> 260 <211> 342 <212> PRT <213> E. Coli

<400> 260

 Met
 Leu
 Lys
 Phe
 Ile
 Glr
 Asn
 Asn
 Arg
 Glu
 Ile
 Thr
 Ala
 Leu
 Leu
 Phe
 Leu
 Phe
 Ile
 Ile</th

Pro Ala Glu Leu Lys Gln Leu Ser Ala Pro Leu Leu Gly Val Ser 150 155 Ala Ile Gly Trp Leu Thr Ile Ile Leu Val Ala Phe Met Ala Trp Leu 165 170 175 Leu Ala Lys Thr Ala Phe Gly Arg Ser Phe Tyr Ala Thr Gly Asp Asn 180 185 190 Leu Gln Gly Ala Arg Gln Leu Gly Val Arg Thr Glu Ala Ile Arg Ile 195 200 205 Val Ala Phe Ser Leu Asn Gly Cys Met Ala Ala Leu Ala Gly Ile Val 210 215 220 Phe Ala Ser Gln Ile Gly Phe Ile Pro Asn Gln Thr Gly Thr Gly Leu 225 230 230 235 240 Glu Met Lys Ala Ile Ala Ala Cys Val Leu Gly Gly Ile Ser Leu Leu 245 250 255 Gly Gly Ser Gly Ala Ile Ile Gly Ala Val Leu Gly Ala Trp Phe Leu 260 265 270 Thr Gln Ile Asp Ser Val Leu Val Leu Leu Arg Ile Pro Ala Trp Trp 275 280 285 Asn Asp Phe Ile Ala Gly Leu Val Leu Leu Ala Val Leu Val Phe Asp 290 295 300 Gly Arg Leu Arg Cys Ala Leu Glu Arg Asn Leu Arg Arg Gln Lys Tyr 305 310 315 320 Ala Arg Phe Met Thr Pro Pro Pro Ser Val Lys Pro Ala Ser Ser Gly 325 330 Lys Lys Arg Glu Ala Ala 340

<210> 261 <211> 330 <212> PRT <213> E. Coli

Ala Ala Val Leu Leu Val Ser Tyr Phe Gly Ser Ala Arg Ser Asp Leu 240

Gly Ala Ser Phe Leu Met Pro Ala Ile Thr Ala Val Val Leu Gly Gly 255

Ala Asn Ile Tyr Gly Gly Ser Gly Ser Ile Ile Gly Thr Ala Ile Ala 265

Val Leu Leu Val Gly Tyr Leu Gln Gln Gly Leu Gln Met Ala Gly Val 270

Pro Asn Gln Val Ser Ser Ala Leu Ser Gly Ala Leu Leu Ile Val Val 290

Val Val Gly Arg Ser Val Ser Leu His Arg Gln Gln Ile Lys Glu Trp 305

Leu Ala Arg Arg Ala Asn Pro Leu Pro 335

<210> 262 <211> 340 <212> PRT <213> E. Coli

<400> 262 Met Thr Leu His Arg Phe Lys Lys Ile Ala Leu Leu Ser Ala Leu Gly
1 5 10 15 Ile Ala Ala Ile Ser Met As
n Val Gl
n Ala Ala Glu Arg Ile Ala Phe $20 \hspace{1.5cm} 25 \hspace{1.5cm} 30 \hspace{1.5cm}$ Ile Pro Lys Leu Val Gly Val Gly Phe Phe Thr Ser Gly Gly Asn Gly 35 40 45 Ala Gln Gln Ala Gly Lys Glu Leu Gly Val Asp Val Thr Tyr Asp Gly 50 55 60 Pro Thr Glu Pro Ser Val Ser Gly Gln Val Gln Leu Ile Asn Asn Phe 65 70 75 80 Val Asn Gln Gly Tyr Asn Ala Ile Ile Val Ser Ala Val Ser Pro Asp 85 90 95 Gly Leu Cys Pro Ala Leu Lys Arg Ala Met Gln Arg Gly Val Arg Val 100 . 105 110Leu Thr Trp Asp Ser Asp Thr Lys Pro Glu Cys Arg Ser Tyr Tyr Ile 115 120 125 Asn Gln Gly Thr Pro Ala Gln Leu Gly Gly Met Leu Val Asp Met Ala 130 135 140 Ala Arg Gln Val Asn Lys Asp Lys Ala Lys Val Ala Phe Phe Tyr Ser 145 150 155 160 Ser Pro Thr Val Thr Asp Gln Asn Gln Trp Val Lys Glu Ala Lys Ala 165 170 175 Lys Ile Ala Lys Glu His Pro Gly Trp Glu Ile Val Thr Thr Gln Phe 180 185 190 Gly Tyr Asn Asp Ala Thr Lys Ser Leu Gln Thr Ala Glu Gly Ile Leu 195 200 205 Lys Ala Tyr Ser Asp Leu Asp Ala Ile Ile Ala Pro Asp Ala Asn Ala 210 - 215 220 Leu Pro Ala Ala Ala Gln Ala Ala Glu Asn Leu Lys Asn Asp Lys Val 225 230 235 240 Ala Ile Val Gly Phe Ser Thr Pro Asn Val Met Arg Pro Tyr Val Glu 245 250 255 Arg Gly Thr Val Lys Glu Phe Gly Leu Trp Asp Val Val Gln Gln Gly 260 265 270 Lys Ile Ser Val Tyr Val Ala Asp Ala Leu Leu Lys Lys Gly Ser Met 275 280 285 Lys Thr Gly Asp Lys Leu Asp Ile Lys Gly Val Gly Gln Val Glu Val

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295
Ser Pro Asn Ser Val Gln Gly Tyr Asp Tyr Glu Ala Asp Gly Asn Gly 305 310 315 320
Ile Val Leu Leu Pro Glu Arg Val Ile Phe Asn Lys Glu Asn Ile Gly
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                                         330
Lys Tyr Asp Phe
              340
       <210> 263
       <211> 291
       <212> PRT
       <213> E. Coli
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Gln Pro Gln Lys Asn Ile Pro Phe Thr Leu Lys Gly Cys Gly Ala Leu 20 25 30
Asp Trp Gly Met Gln Ser Arg Leu Ser Arg Ile Phe Asn Pro Lys Thr 35 \hspace{1cm} 40 \hspace{1cm} 45
Gly Lys Thr Val Met Leu Ala Phe Asp His Gly Tyr Phe Gln Gly Pro 50 60
Thr Thr Gly Leu Glu Arg Ile Asp Ile Asn Ile Ala Pro Leu Phe Glu 65 70 75 80
His Ala Asp Val Leu Met Cys Thr Arg Gly Ile Leu Arg Ser Val Val 85 90 95
Pro Pro Ala Thr Asn Arg Pro Val Val Leu Arg Ala Ser Gly Ala Asn 100 $105$
Ser Ile Leu Ala Glu Leu Ser Asn Glu Ala Val Ala Leu Ser Met Asp
115 120 125
Asp Ala Val Arg Leu Asn Ser Cys Ala Val Ala Ala Gln Val Tyr Ile
130 135 140
Gly Ser Glu Tyr Glu His Gln Ser Ile Lys Asn Ile Ile Gln Leu Val
145 150 155 160
Asp Ala Gly Met Lys Val Gly Met Pro Thr Met Ala Val Thr Gly Val
165 170 175
Gly Lys Asp Met Val Arg Asp Gln Arg Tyr Phe Ser Leu Ala Thr Arg
180 185 190
Ile Ala Ala Glu Met Gly Ala Gln Ile Ile Lys Thr Tyr Tyr Val Glu
195 200 205
Lys Gly Phe Glu Arg Ile Val Ala Gly Cys Pro Val Pro Ile Val Ile
210 215 220

Ala Gly Gly Lys Lys Leu Pro Glu Arg Glu Ala Leu Glu Met Cys Trp
225 230 240
Gln Ala Ile Asp Gln Gly Ala Ser Gly Val Asp Met Gly Arg Asn Ile
245 250 255
Phe Gln Ser Asp His Pro Val Ala Met Met Lys Ala Val Gln Ala Val 260 265 270
Val His His Asn Glu Thr Ala Asp Arg Ala Tyr Glu Leu Tyr Leu Ser
275 280 285
Glu Lys Gln
    290
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 Met
 His
 Val
 Thr
 Leu
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 Glu
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 Asn
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 Asp
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 Asp
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 Leu
 Gly
 Ser
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 Asp
 Ile
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 Gly
 Ser
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 Gly
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 Asp</th

<210> 265 <211> 383 <212> PRT <213> E. Coli

<400> 265 Met Phe Glu Pro Met Glu Leu Thr Asn Asp Ala Val Ile Lys Val Ile 10 Gly Val Gly Gly Gly Gly Asn Ala Val Glu His Met Val Arg Glu 25 30 Arg Ile Glu Gly Val Glu Phe Phe Ala Val Asn Thr Asp Ala Gln Ala 35 40 45 Leu Arg Lys Thr Ala Val Gly Gln Thr Ile Gln Ile Gly Ser Gly Ile 50 55 60 Thr Lys Gly Leu Gly Ala Gly Ala Asn Pro Glu Val Gly Arg Asn Ala 65 70 75 80 Ala Asp Glu Asp Arg Asp Ala Leu Arg Ala Ala Leu Glu Gly Ala Asp 85 90 95 Met Val Phe Ile Ala Ala Gly Met Gly Gly Gly Thr Gly Thr Gly Ala 100 105 110 Ala Pro Val Val Ala Glu Val Ala Lys Asp Leu Gly Ile Leu Thr Val 115 120 125 Ala Val Val Thr Lys Pro Phe Asn Phe Glu Gly Lys Lys Arg Met Ala 130 135 140 Phe Ala Glu Gln Gly Ile Thr Glu Leu Ser Lys His Val Asp Ser Leu 145 150 155 160 Ile Thr Ile Pro Asn Asp Lys Leu Leu Lys Val Leu Gly Arg Gly Ile 165 170 175 Ser Leu Leu Asp Ala Phe Gly Ala Ala Asn Asp Val Leu Lys Gly Ala 180 185 190 Val Gln Gly Ile Ala Glu Leu Ile Thr Arg Pro Gly Leu Met Asn Val 195 200 205 Asp Phe Ala Asp Val Arg Thr Val Met Ser Glu Met Gly Tyr Ala Met 210 225 220 Met Gly Ser Gly Val Ala Ser Gly Glu Asp Arg Ala Glu Glu Ala Ala 225 230 235 240 Glu Met Ala Ile Ser Ser Pro Leu Leu Glu Asp Ile Asp Leu Ser Gly 245 250 255 Ala Arg Gly Val Leu Val Asn Ile Thr Ala Gly Phe Asp Leu Arg Leu 260 265 270 Asp Glu Phe Glu Thr Val Gly Asn Thr Ile Arg Ala Phe Ala Ser Asp 275 280 285 Asn Ala Thr Val Val Ile Gly Thr Ser Leu Asp Pro Asp Met Asn Asp 290 295 300 Glu Leu Arg Val Thr Val Val Ala Thr Gly Ile Gly Met Asp Lys Arg 310 315 Pro Glu Ile Thr Leu Val Thr Asn Lys Gln Val Gln Gln Pro Val Met

Asp Arg Tyr Gln Gln His Gly Met Ala Pro Leu Thr Gln Glu Gln Lys 340 345 350

Pro Val Ala Lys Val Val Asn Asp Asn Ala Pro Gln Thr Ala Lys Glu 355 366

Pro Asp Tyr Leu Asp Ile Pro Ala Phe Leu Arg Lys Gln Ala Asp 370 370

<210> 266 <211> 1014 <212> PRT <213> E. Coli

<400> 266

Met Asp Val Ser Arg Gln Phe Phe Lys Ile Cys Ala Gly Gly Met 1 5 10 15 Ala Gly Thr Thr Val Ala Ala Leu Gly Phe Ala Pro Lys Gln Ala Leu 20 25 30 Ala Gln Ala Arg Asn Tyr Lys Leu Leu Arg Ala Lys Glu Ile Arg Asn $35 \hspace{1cm} 40 \hspace{1cm} 45$ Thr Cys Thr Tyr Cys Ser Val Gly Cys Gly Leu Leu Met Tyr Ser Leu 50 60Gly Asp Gly Ala Lys Asn Ala Arg Glu Ala Ile Tyr His Ile Glu Gly 65 70 75 80 Asp Pro Asp His Pro Val Ser Arg Gly Ala Leu Cys Pro Lys Gly Ala 85 90 95 Gly Leu Leu Asp Tyr Val Asn Ser Glu Asn Arg Leu Arg Tyr Pro Glu 100 105 110 Tyr Arg Ala Pro Gly Ser Asp Lys Trp Gln Arg Ile Ser Trp Glu Glu 115 120 125 Ala Phe Ser Arg Ile Ala Lys Leu Met Lys Ala Asp Arg Asp Ala Asn 130 135 140 Phe Ile Glu Lys Asn Glu Gln Gly Val Thr Val Asn Arg Trp Leu Ser 145 150 155 160 Thr Gly Met Leu Cys Ala Ser Gly Ala Ser Asn Glu Thr Gly Met Leu 165 170 175 Thr Gln Lys Phe Ala Arg Ser Leu Gly Met Leu Ala Val Asp Asn Gln 180 185 190 Ala Arg Val His Gly Pro Thr Val Ala Ser Leu Ala Pro Thr Phe Gly 195 200 205 Arg Gly Ala Met Thr Asn His Trp Val Asp Ile Lys Asn Ala Asn Val 210 225 220 Val Met Val Met Gly Gly Asn Ala Ala Glu Ala His Pro Val Gly Phe 225 230 235 240 Arg Trp Ala Met Glu Ala Lys Asn Asn Asn Asp Ala Thr Leu Ile Val 245 250 255 Val Asp Pro Arg Phe Thr Arg Thr Ala Ser Val Ala Asp Ile Tyr Ala 260 265 270 Pro Ile Arg Ser Gly Thr Asp Ile Thr Phe Leu Ser Gly Val Leu Arg 275 280 285 Tyr Leu Ile Glu Asn Asn Lys Ile Asn Ala Glu Tyr Val Lys His Tyr 290 295 300 Thr Asn Ala Ser Leu Leu Val Arg Asp Asp Phe Ala Phe Glu Asp Gly 305 310 315 320 Leu Phe Ser Gly Tyr Asp Ala Glu Lys Arg Gln Tyr Asp Lys Ser Ser 325 330 335 Trp Asn Tyr Gln Leu Asp Glu Asn Gly Tyr Ala Lys Arg Asp Glu Thr 340 345 350 Leu Thr His Pro Arg Cys Val Trp Asn Leu Leu Lys Glu His Val Ser 360

Arg Tyr Thr Pro Asp Val Val Glu Asn Ile Cys Gly Thr Pro Lys Ala 370 375 380 380 Asp Phe Leu Lys Val Cys Glu Val Leu Ala Ser Thr Ser Ala Pro Asp 385 390 395 400 Arg Thr Thr Thr Phe Leu Tyr Ala Leu Gly Trp Thr Gln His Thr Val 405 410 415 Gly Ala Gln Asn Ile Arg Thr Met Ala Met Ile Gin Leu Leu Gly 420 425 430 Asn Met Gly Met Ala Gly Gly Gly Val Asn Ala Leu Arg Gly His Ser Asn Ile Gln Gly Leu Thr Asp Leu Gly Leu Leu Ser Thr Ser Leu Pro 450 455 460 Gly Tyr Leu Thr Leu Pro Ser Glu Lys Gln Val Asp Leu Gln Ser Tyr 465 470 475 480 Leu Glu Ala Asn Thr Pro Lys Ala Thr Leu Ala Asp Gln Val Asn Tyr 485 490 495 Trp Ser Asn Tyr Pro Lys Phe Phe Val Ser Leu Met Lys Ser Phe Tyr 500 505 510 Gly Asp Ala Ala Gln Lys Glu Asn Asn Trp Gly Tyr Asp Trp Leu Pro 515 520 525 Lys Trp Asp Gln Thr Tyr Asp Val Ile Lys Tyr Phe Asn Met Met Asp 530 540 Glu Gly Lys Val Thr Gly Tyr Phe Cys Gln Gly Phe Asn Pro Val Ala 545 550 555 560 Ser Phe Pro Asp Lys Asn Lys Val Val Ser Cys Leu Ser Lys Leu Lys 565 570 575 Tyr Met Val Val Ile Asp Pro Leu Val Thr Glu Thr Ser Thr Phe Trp 580 585 590 Gln Asn His Gly Glu Ser Asn Asp Val Asp Pro Ala Ser Ile Gln Thr 595 600 605 Glu Val Phe Arg Leu Pro Ser Thr Cys Phe Ala Glu Glu Asp Gly Ser 610 615 620 Ile Ala Asn Ser Gly Arg Trp Leu Gln Trp His Trp Lys Gly Gln Asp 625 630 635 640 Ala Pro Gly Glu Ala Arg Asn Asp Gly Glu Ile Leu Ala Gly Ile Tyr 645 650 655 His His Leu Arg Glu Leu Tyr Gln Ser Glu Gly Gly Lys Gly Val Glu 660 665 670 Pro Leu Met Lys Met Ser Trp Asn Tyr Lys Gln Pro His Glu Pro Gln 675 680 685 Ser Asp Glu Val Ala Lys Glu Asn Asn Gly Tyr Ala Leu Glu Asp Leu 690 695 700 Tyr Asp Ala Asn Gly Val Leu Ile Ala Lys Lys Gly Gln Leu Leu Ser 705 710 715 720 Ser Phe Ala His Leu Arg Asp Asp Gly Thr Thr Ala Ser Ser Cys Trp 725 730 730 Ile Tyr Thr Gly Ser Trp Thr Glu Gln Gly Asn Gln Met Ala Asn Arg
740 745 750 Asp Asn Ser Asp Pro Ser Gly Leu Gly Asn Thr Leu Gly Trp Ala Trp 755 760 765 Ala Trp Pro Leu Asn Arg Arg Val Leu Tyr Asn Arg Ala Ser Ala Asp 770 775 780 Iie Asn Gly Lys Pro Trp Asp Pro Lys Arg Met Leu Ile Gln Trp Asn 785 790 795 800 Gly Ser Lys Trp Thr Gly Asn Asp Ile Pro Asp Phe Gly Asn Ala Ala 805 810 815 Pro Gly Thr Pro Thr Gly Pro Phe Ile Met Gln Pro Glu Gly Met Gly 820 825 830 Arg Leu Phe Ala Ile Asn Lys Met Ala Glu Gly Pro Phe Pro Glu His 835 840 845 845 Tyr Glu Pro Ile Glu Thr Pro Leu Gly Thr Asn Pro Leu His Pro Asn

850 855 860 Val Val Ser Asn Pro Val Val Arg Leu Tyr Glu Gln Asp Ala Leu Arg 865 870 875 880 Met Gly Lys Lys Glu Gln Phe Pro Tyr Val Gly Thr Thr Tyr Arg Leu 885 890 895 Thr Glu His Phe His Thr Trp Thr Lys His Ala Leu Leu Asn Ala Ile 900 905 910 Ala Gln Pro Glu Gln Phe Val Glu Ile Ser Glu Thr Leu Ala Ala Ala 915 920 925 Lys Gly Ile Asn Asn Gly Asp Arg Val Thr Val Ser Ser Lys Arg Gly 930 935 940 Phe Ile Arg Ala Val Ala Val Val Thr Arg Arg Leu Lys Pro Leu Asn 945 950 955 960 Val Asn Gly Gln Gln Val Glu Thr Val Gly Ile Pro Ile His Trp Gly
965 970 975 Phe Glu Gly Val Ala Arg Lys Gly Tyr Ile Ala Asn Thr Leu Thr Pro 980 985 990 Asn Val Gly Asp Ala Asn Ser Gln Thr Pro Glu Tyr Lys Ala Phe Leu 1000 1005 Val Asn Ile Glu Lys Ala 1010

<210> 267 <211> 294 <212> PRT <213> E. Coli

<400> 267 Met Ala Met Glu Thr Gln Asp Ile Ile Lys Arg Ser Ala Thr Asn Ser 1 10 55 10 15 $^{\circ}$ Ile Thr Pro Pro Ser Gln Val Arg Asp Tyr Lys Ala Glu Val Ala Lys 20 25 30 Leu Ile Asp Val Ser Thr Cys Ile Gly Cys Lys Ala Cys Gln Val Ala 35 40 45 Cys Ser Glu Trp Asn Asp Ile Arg Asp Glu Val Gly His Cys Val Gly 50 60 Val Tyr Asp Asn Pro Ala Asp Leu Ser Ala Lys Ser Trp Thr Val Met 65 70. 75 80 Arg Phe Ser Glu Thr Glu Gln Asn Gly Lys Leu Glu Trp Leu Ile Arg 85 90 95 Lys Asp Gly Cys Met His Cys Glu Asp Pro Gly Cys Leu Lys Ala Cys 100 105 110 Pro Ser Ala Gly Ala Ile Ile Gln Tyr Ala Asn Gly Ile Val Asp Phe 115 120 125 Gln Ser Glu Asn Cys Ile Gly Cys Gly Tyr Cys Ile Ala Gly Cys Pro 130 135 140 Phe Asn Ile Pro Arg Leu Asn Lys Glu Asp Asn Arg Val Tyr Lys Cys
145 150 155 160

Thr Leu Cys Val Asp Arg Val Ser Val Gly Gln Glu Pro Ala Cys Val
165 170 175 Lys Thr Cys Pro Thr Gly Ala Ile His Phe Gly Thr Lys Lys Glu Met 180 185 190 Leu Glu Leu Ala Glu Gln Arg Val Ala Lys Leu Lys Ala Arg Gly Tyr 195 200 205 Glu His Ala Gly Val Tyr Asn Pro Glu Gly Val Gly Gly Thr His Val 210 225 Met Tyr Val Leu His His Ala Asp Gln Pro Glu Leu Tyr His Gly Leu 225 230 235 240 Pro Lys Asp Pro Lys Ile Asp Thr Ser Val Ser Leu Trp Lys Gly Ala 245 250 255

Leu Lys Pro Leu Ala Ala Ala Gly Phe Ile Ala Thr Phe Ala Gly Leu

260 265 270

Ile Phe His Tyr Ile Gly Ile Gly Pro Asn Lys Glu Val Asp Asp Asp 275 280 285

Glu Glu Asp His His Glu 290

<210> 268 <211> 217 <212> PRT <213> E. Coli

<400> 268 Met Ser Lys Ser Lys Met Ile Val Arg Thr Lys Phe Ile Asp Arg Ala 1 5 10 15 Cys His Trp Thr Val Val Ile Cys Phe Phe Leu Val Ala Leu Ser Gly 20 25 30 Ile Ser Phe Phe Phe Pro Thr Leu Gln Trp Leu Thr Gln Thr Phe Gly 35 40 45 Thr Pro Gln Met Gly Arg Ile Leu His Pro Phe Phe Gly Ile Ala Ile 50 55 60 Phe Val Ala Leu Met Phe Met Phe Val Arg Phe Val His His Asn Ile 65 70 75 80 Pro Asp Lys Lys Asp Ile Pro Trp Leu Leu Asn Ile Val Glu Val Leu 85 90 95 Lys Gly Asn Glu His Lys Val Ala Asp Val Gly Lys Tyr Asn Ala Gly 100 105 110 Gln Lys Met Met Phe Trp Ser Ile Met Ser Met Ile Phe Val Leu Leu 115 120 125 Val Thr Gly Val Ile Ile Trp Arg Pro Tyr Phe Ala Gln Tyr Phe Pro 130 135 140 130 Met Gln Val Val Arg Tyr Ser Leu Leu Ile His Ala Ala Ala Gly Ile 145 150 150 160 Ile Leu Ile His Ala Ile Leu Ile His Met Tyr Met Ala Phe Trp Val 165 170 175 Lys Gly Ser Ile Lys Gly Met Ile Glu Gly Lys Val Ser Arg Arg Trp 180 185 190 Ala Lys Lys His His Pro Arg Trp Tyr Arg Glu Ile Glu Lys Ala Glu 195 200 205 Ala Lys Lys Glu Ser Glu Glu Gly Ile 210

> <210> 269 <211> 86 <212> PRT <213> E. Coli

 <400> 269

 Met
 Ala Leu
 Leu
 Ile
 Thr
 Lys
 Lys
 Cys
 Ile
 Asn
 Cys
 Asp
 Met
 Cys_Glu

 Pro
 Glu
 Cys
 Pro
 Asn
 Glu
 Ala
 Ile
 Ser
 Met
 Gly
 Asp
 His
 Ile
 Tyr
 Glu

 Ile
 Asn
 Ser
 Asp
 Lys
 Cys
 Thr
 Glu
 Cys
 Val
 Gly
 His
 Tyr
 Glu
 Thr
 Pro

 35
 40
 40
 45
 45
 45
 Tyr
 Asp
 Pro

 50
 55
 55
 60
 60
 Asp
 Phe
 Val
 Leu
 Met

 65
 70
 75
 75
 80
 Asp
 Lys
 80

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<211> 400
       <212> PRT
       <213> E. Coli
       <400> 270
Met Gln Ser Val Asp Val Ala Ile Val Gly Gly Gly Met Val Gly Leu 1 5 10 15
Ala Val Ala Cys Gly Leu Gln Gly Ser Gly Leu Arg Val Ala Val Leu
20 25 30
Glu Gln Arg Val Gln Glu Pro Leu Ala Ala Asn Ala Pro Pro Gln Leu
35 40 45
Arg Val Ser Ala Ile Asn Ala Ala Ser Glu Lys Leu Leu Thr Arg Leu 50 55 60
Gly Val Trp Gln Asp Ile Leu Ser Arg Arg Ala Ser Cys Tyr His Gly 65 70 75 80
Met Glu Val Trp Asp Lys Asp Ser Phe Gly His Ile Ser Phe Asp Asp 90 95
Gln Ser Met Gly Tyr Ser His Leu Gly His Ile Val Glu Asn Ser Val
100 105 110
Ile His Tyr Ala Leu Trp Asn Lys Ala His Gln Ser Ser Asp Ile Thr
115 120 125
Leu Leu Ala Pro Ala Glu Leu Gln Gln Val Ala Trp Gly Glu Asn Glu
130 135 140
Thr Phe Leu Thr Leu Lys Asp Gly Ser Met Leu Thr Ala Arg Leu Val
145 150 155 160
Ile Gly Ala Asp Gly Ala Asn Ser Trp Leu Arg Asn Lys Ala Asp Ile
165 170 175
Pro Leu Thr Phe Trp Asp Tyr Gln His His Ala Leu Val Ala Thr Ile
180 185 190
Arg Thr Glu Glu Pro His Asp Ala Val Ala Arg Gln Val Phe His Gly 195 200 205
Glu Gly Ile Leu Ala Phe Leu Pro Leu Ser Asp Pro His Leu Cys Ser
210 215 220
Ile Val Trp Ser Leu Ser Pro Glu Glu Ala Gln Arg Met Gln Gln Ala
225 230 235 240
Ser Glu Asp Glu Phe Asn Arg Ala Leu Asn Ile Ala Fhe Asp Asn Arg
245 250 255
Leu Gly Leu Cys Lys Val Glu Ser Ala Arg Gln Val Phe Pro Leu Thr 260 265 270
Gly Arg Tyr Ala Arg Gln Phe Ala Ser His Arg Leu Ala Leu Val Gly 275 280 285
Asp Ala Ala His Thr Ile His Pro Leu Ala Gly Gln Gly Val Asn Leu
290 295 300
Gly Phe Met Asp Ala Ala Glu Leu Ile Ala Glu Leu Lys Arg Leu His 305 310 315 320
Arg Gln Gly Lys Asp Ile Gly Gln Tyr Ile Tyr Leu Arg Arg Tyr Glu 325 330 335
Arg Ser Arg Lys His Sor Ala Ala Leu Met Leu Ala Gly Met Gln Gly 340 345 350

Phe Arg Asp Leu Phe Ser Gly Thr Asn Pro Ala Lys Lys Leu Leu Arg 355 360 365
Asp Ile Gly Leu Lys Leu Ala Asp Thr Leu Pro Gly Val Lys Pro Gln 370 380
Leu Ile Arg Gln Ala Met Gly Leu Asn Asp Leu Pro Glu Trp Leu Arg
                        390
                                                395
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<210> 271

<210> 270

<211> 392 <212> PRT <213> E. Coli

<400> 271 Met Ser Val Ile Ile Val Gly Gly Gly Met Ala Gly Ala Thr Leu Ala 1 5 10 15 Leu Ala Ile Ser Arg Leu Ser His Gly Ala Leu Pro Val His Leu Ile $20 \hspace{1cm} 25 \hspace{1cm} 30$ Glu Ala Thr Ala Pro Glu Ser His Ala His Pro Gly Phe Asp Gly Arg 35 40 45 Ala Ile Ala Leu Ala Ala Gly Thr Cys Gln Gln Leu Ala Arg Ile Gly 50 55 60 Val Trp Gln Ser Leu Ala Asp Cys Ala Thr Ala Ile Thr Thr Val His 65 70 75 80 Val Ser Asp Arg Gly His Ala Gly Phe Val Thr Leu Ala Ala Glu Asp 85 90 95 Tyr Gln Leu Ala Ala Leu Gly Gln Val Val Glu Leu His Asn Val Gly 100 105 110 Gln Arg Leu Phe Ala Leu Leu Arg Lys Ala Pro Gly Val Thr Leu His 115 120 125 Cys Pro Asp Arg Val Ala Asn Val Ala Arg Thr Gln Ser His Val Glu 130 135 140 Val Thr Leu Glu Ser Gly Glu Thr Leu Thr Gly Arg Val Leu Val Ala 145 150 160

Ala Asp Gly Thr His Ser Ala Leu Ala Thr Ala Cys Gly Val Asp Trp 165 170 175 Gln Glu Pro Tyr Glu Gln Leu Ala Val Ile Ala Asn Val Ala Thr 180 185 190 Ser Val Ala His Glu Gly Arg Ala Phe Glu Arg Phe Thr Gln His Gly 195 200 205 Pro Leu Ala Met Leu Pro Met Ser Asp Gly Arg Cys Ser Leu Val Trp 210 215 220 Cys His Pro Leu Glu Arg Arg Glu Glu Val Leu Ser Trp Ser Asp Glu 225 230 235 240 Lys Phe Cys Arg Glu Leu Gln Ser Ala Phe Gly Trp Arg Leu Gly Lys 245 250 255

 Ile Thr His Ala Gly Lys Arg Ser Ala Tyr Pro Leu Ala Leu Thr His 260
 265
 270

 Ala Ala Arg Ser Ile Thr His Arg Thr Val Leu Val Gly Asn Ala Ala 275
 280
 285

 Gln Thr Leu His Pro Ile Ala Gly Gln Gly Phe Asn Leu Gly Met Arg 290 295 300 Asp Val Met Ser Leu Ala Glu Thr Leu Thr Gln Ala Gln Glu Arg Gly 305 310 315 320 Glu Asp Met Gly Asp Tyr Gly Val Leu Cys Arg Tyr Gln Gln Arg Arg 325 330 335 Gln Ser Asp Arg Glu Ala Thr Ile Gly Val Thr Asp Ser Leu Val His 340 345 Leu Phe Ala Asn Arg Trp Ala Pro Leu Val Val Gly Arg Asn Ile Gly 355 360 365 Leu Met Thr Met Glu Leu Phe Thr Pro Ala Arg Asp Val Leu Ala Gln 370 375 380 Arg Thr Leu Gly Trp Val Ala Arg 385 390

<210> 272 <211> 441 <212> PRT <213> E. Coli

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<400> 272
Met Ser Glu Ile Ser Arg Gln Glu Phe Gln Arg Arg Arg Gln Ala Leu
                                         10
Val Glu Gln Met Gln Pro Gly Ser Ala Ala Leu Ile Phe Ala Ala Pro
20 25 30
Glu Val Thr Arg Ser Ala Asp Ser Glu Tyr Pro Tyr Arg Gln Asn Ser
35 40 45
Asp Phe Trp Tyr Phe Thr Gly Phe Asn Glu Pro Glu Ala Val Leu Val 50 55 60
Leu Ile Lys Ser Asp Asp Thr His Asn His Ser Val Leu Phe Asn Arg 65 70 75 80
Val Arg Asp Leu Thr Ala Glu Ile Trp Phe Gly Arg Arg Leu Gly Gln
85 90 95
Asp Ala Ala Pro Glu Lys Leu Gly Val Asp Arg Ala Leu Ala Phe Ser
100 105 110
Glu Ile Asn Gln Gln Leu Tyr Gln Leu Leu Asn Gly Leu Asp Val Val 115 120 125
Tyr His Ala Gln Gly Glu Tyr Ala Tyr Ala Asp Val Ile Val Asn Ser
130 135 140
Ala Leu Glu Lys Leu Arg Lys Gly Ser Arg Gln Asn Leu Thr Ala Pro
145 150 155 160
Ala Thr Met Ile Asp Trp Arg Pro Val Val His Glu Met Arg Leu Phe
165 170 175
Lys Ser Pro Glu Glu Ile Ala Val Leu Arg Arg Ala Gly Glu Ile Thr
180 185 190
Ala Met Ala His Thr Arg Ala Met Glu Lys Cys Arg Pro Gly Met Phe
195 200 205
Glu Tyr His Leu Glu Gly Glu Ile His His Glu Phe Asn Arg His Gly 210 215 220
Ala Arg Tyr Pro Ser Tyr Asn Thr Ile Val Gly Ser Gly Glu Asn Gly 225 230 235 240
Cys Ile Leu His Tyr Thr Glu Asn Glu Cys Glu Met Arg Asp Gly Asp 245 250 255
Leu Val Leu Ile Asp Ala Gly Cys Glu Tyr Lys Gly Tyr Ala Gly Asp 260 265 270
Ile Thr Arg Thr Phe Pro Val Asn Gly Lys Phe Thr Gln Ala Gln Arg 275 . 280 285
Glu Ile Tyr Asp Ile Val Leu Glu Ser Leu Glu Thr Ser Leu Arg Leu
290 295 300
Tyr Arg Pro Gly Thr Ser Ile Leu Glu Val Thr Gly Glu Val Val Arg 305 310 315 320
Ile Met Val Ser Gly Leu Val Lys Leu Gly Ile Leu Lys Gly Asp Val
325 330 335
Asp Glu Leu Ile Ala Gln Asn Ala His Arg Pro Phe Phe Met His Gly 340 345 . 350
Leu Ser His Trp Leu Gly Leu Asp Val His Asp Val Gly Val Tyr Gly 355 360 365
Gln Asp Arg Ser Arg Ile Leu Glu Pro Gly Met Val Leu Thr Val Glu
370 375 380
Pro Gly Leu Tyr Ile Ala Pro Asp Ala Glu Val Pro Glu Gln Tyr Arg
385 390 395 400
Gly Ile Gly Ile Arg Ile Glu Asp Asp Ile Val Ile Thr Glu Thr Gly
405 410 415
Asn Glu Asn Leu Thr Ala Ser Val Val Lys Lys Pro Glu Glu Ile Glu
                                   425
            420
Ala Leu Met Val Ala Ala Arg Lys Gln
         435
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<210> 273

<211> 194 <212> PRT <213> E. Coli

<400> 273 Met Leu Met Ser Ile Gln Asn Glu Met Pro Gly Tyr Asn Glu Met Asn 5 10 15 Gln Tyr Leu Asn Gln Gln Gly Thr Gly Leu Thr Pro Ala Glu Met His 20 25 30 Gly Leu Ile Ser Gly Met Ile Cys Gly Gly Asn Asp Asp Ser Ser Trp 35 40 45 Leu Pro Leu Leu His Asp Leu Thr Asn Glu Gly Met Ala Phe Gly His 50 55 60 Glu Leu Ala Gln Ala Leu Arg Lys Met His Ser Ala Thr Ser Asp Ala 65 70 75 80 Leu Gln Asp Asp Gly Phe Leu Phe Gln Leu Tyr Leu Pro Asp Gly Asp 85 90 95 Asp Val Ser Val Phe Asp Arg Ala Asp Ala Leu Ala Gly Trp Val Asn 100 105 110 His Phe Leu Leu Gly Leu Gly Val Thr Gln Pro Lys Leu Asp Lys Val Thr Gly Glu Thr Gly Glu Ala Ile Asp Asp Leu Arg Asn Ile Ala Gln
130 135 140 Leu Gly Tyr Asp Glu Asp Glu Asp Gln Glu Glu Leu Glu Met Ser Leu 145 150 155 160 Glu Glu Ile Ile Glu Tyr Val Arg Val Ala Ala Leu Leu Cys His Asp 165 170 175 Thr Phe Thr His Pro Gln Pro Thr Ala Pro Glu Val Gln Lys Pro Thr 180 185 190 Leu His

<210> 274 <211> 120 <212> PRT <213> E. Coli

<400> 274

 Met lust
 Lys
 Leu lust
 Phe lust
 Ala lust
 Tyr
 Thr lust
 Ser lust
 Ile lust
 Gly lust
 Val lust
 Ala lust
 Ala lust
 Ala lust
 Phe lust
 Ala l

Val Thr Phe Ser Ala Ile Ser Leu Val Cys Gly Phe Val Tyr Ser Lys 100 105 110 Phe Ile Val Phe Arg Asp Ala Lys

<210> 275 <211> 306 <212> PRT <213> E. Coli

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<400> 275
Met Lys Ile Ser Leu Val Val Pro Val Phe Asn Glu Glu Glu Ala Ile
                                          10
Pro Ile Phe Tyr Lys Thr Val Arg Glu Phe Glu Glu Leu Lys Ser Tyr
20 25 30
                                    25
Glu Val Glu Ile Val Phe Ile Asn Asp Gly Ser Lys Asp Ala Thr Glu
35 40 45
Ser Ile Ile Asn Ala Leu Ala Val Ser Asp Pro Leu Val Val Pro Leu
50 55 60
Ser Phe Thr Arg Asn Phe Gly Lys Glu Pro Ala Leu Phe Ala Gly Leu
65 70 75 80
Asp His Ala Thr Gly Asp Ala Ile Ile Pro Ile Asp Val Asp Leu Gln
85 90 95
Asp Pro Ile Glu Val Ile Pro His Leu Ile Glu Lys Trp Gln Ala Gly 100 105 110
Ala Asp Met Val Leu Ala Lys Arg Ser Asp Arg Ser Thr Asp Gly Arg 115 120 125
Leu Lys Arg Lys Thr Ala Glu Trp Phe Tyr Lys Leu His Asn Lys Ile
130 135 140
Ser Asn Pro Lys Ile Glu Glu Asn Val Gly Asp Phe Arg Leu Met Ser 145 150 155 160
Arg Asp Val Val Glu Asn Ile Lys Leu Met Pro Glu Arg Asn Leu Phe
165 170 175
Met Lys Gly Ile Leu Ser Trp Val Gly Gly Lys Thr Asp Ile Val Glu
180 185 190
Tyr Val Arg Ala Glu Arg Ile Ala Gly Asp Thr Lys Phe Asn Gly Trp
195 200 205
Lys Leu Trp Asn Leu Ala Leu Glu Gly Ile Thr Ser Phe Ser Thr Phe 210 215 220
                                                  220
Pro Leu Arg Ile Trp Thr Tyr Ile Gly Leu Val Val Ala Ser Val Ala
225 230 235 240
Phe Ile Tyr Gly Ala Trp Met Ile Leu Asp Thr Ile Ile Phe Gly Asn 245 250 255
Ala Val Arg Gly Tyr Pro Ser Leu Leu Val Ser Ile Leu Phe Leu Gly 260 265 270
Gly Ile Gln Met Ile Gly Ile Gly Val Leu Gly Glu Tyr Ile Gly Arg
275 280 285
Thr Tyr Ile Glu Thr Lys Lys Arg Pro Lys Tyr Ile Ile Lys Arg Val
    290
                           295
                                                   300
Lys Lys
305
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<210> 276 <211> 443 <212> PRT <213> E. Coli

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Leu Phe Leu Lys Val Ile Tyr Ile Tyr Ser Leu Tyr Ala Ile Phe Thr 100 105 110
Ser Tyr Ile Lys Thr Glu Arg Tyr Val Thr Leu Phe Thr Phe Phe Ile
115 120 125
Leu Ala Phe Leu Met Cys Ser Ser Ser Thr Leu Ser Met Phe Ala Ser
130 135 140
Phe Tyr Gln Glu Gln Ile Val Ile Ile Phe Leu Pro Phe Leu Val Tyr
145 150 155 160
Ser Leu Thr Cys Lys Asn Asn Lys Ser Met Leu Leu Phe Phe Ser
165 170 175
Leu Leu Ile Ile Ser Thr Ala Lys Asn Gln Phe Ile Leu Thr Pro Leu 180 185 190
Ile Val Tyr Ser Tyr Tyr Ile Phe Phe Asp Arg His Lys Leu Ile Ile
195 200 205
Lys Ser Val Ile Cys Val Val Cys Leu Leu Ala Ser Ile Phe Ala Ile
210 215 220
Ser Tyr Ser Lys Gly Val Val Glu Leu Asn Lys Tyr His Ala Thr Tyr
225 230 235 240
Phe Gly Ser Tyr Leu Tyr Met Lys Asn Asn Gly Tyr Lys Met Pro Ser
245 250 255
Tyr Val Asp Asp Lys Cys Val Gly Leu Asp Ala Trp Gly Asn Lys Phe
260 265 270
Asp Ile Ser Phe Gly Ala Thr Pro Thr Glu Val Gly Thr Glu Cys Phe 275 280 285
Glu Ser His Lys Asp Glu Thr Phe Ser Asn Ala Leu Phe Leu Leu Val
290 295 300
Ser Lys Pro Ser Thr Ile Phe Lys Leu Pro Phe Asp Asp Gly Val Met 305 310 315 320
                   310
Ser Gln Tyr Lys Glu Asn Tyr Phe His Val Tyr Lys Lys Leu His Val
325 330 335
Ile Tyr Gly Glu Ser Asn Ile Leu Thr Thr Ile Thr Asn Ile Lys Asp 340 \hspace{1.5cm} 345 \hspace{1.5cm} 350 \hspace{1.5cm}
Asn Ile Phe Lys Asn Ile Arg Phe Ile Ser Leu Leu Phe Phe Ile 355 360 365
Ala Ser Ile Phe Ile Arg Asn Asn Lys Ile Lys Ala Ser Leu Phe Val
370 375 380
Val Ser Leu Phe Gly Ile Ser Gln Phe Tyr Val Ser Phe Phe Gly Glu
           390
                                           395
Gly Tyr Arg Asp Leu Ser Lys His Leu Phe Gly Met Tyr Phe Ser Phe
405 410 415
Asp Leu Cys Leu Tyr Ile Thr Val Val Phe Leu Ile Tyr Lys Ile Ile
                          425
           420
Gln Arg Asn Gln Asp Asn Ser Asp Val Lys His
         435
                                440
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<210> 277 <211> 82 <212> PRT <213> E. Coli

Val Ala Val Ile Gly Ala Ile Val Val Leu Phe Ile Tyr Arg Lys Ile 65 70 75 80 Lys Ser

<210> 278 <211> 60 <212> PRT <213> E. Coli

<210> 279 <211> 119 <212> PRT <213> E. Coli

 400>
 279

 Met Leu Gln
 Ile
 Pro
 Gln
 Asn
 Tyr
 Ile
 His
 Thr
 Arg
 Ser
 Thr
 Pro
 Phe

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 15
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<210> 280 <211> 246 <212> PRT <213> E. Coli

<210> 281 <211> 464 <212> PRT <213> E. Coli

(213) 2. 00

<400> 281 Met Leu Leu Asp Ala Cys Ser Gln Met Cys Pro Ser Phe Arg Arg Phe Gln Thr Val Phe His Asn Ser Ser Ile Phe Leu Pro Tyr Trp Leu 20 25 30 Ala Thr Leu Val Ser Phe Arg Glu Thr Phe Gln Glu Glu Lys Leu Leu 35 40 45 Thr Met Lys Gly Ser Tyr Lys Ser Arg Trp Val Ile Val Ile Val Val 50 55 60 Val Ile Ala Ala Ile Ala Ala Phe Trp Phe Trp Gin Gly Arg Asn Asp 65 70 75 80 Ser Arg Ser Ala Ala Pro Gly Ala Thr Lys Gln Ala Gln Gln Ser Pro 85 . 90 95 Ala Gly Gly Arg Arg Gly Met Arg Ser Gly Pro Leu Ala Pro Val Gln 100 105 110Ala Ala Thr Ala Val Glu Gln Ala Val Pro Arg Tyr Leu Thr Gly Leu 115 120 125 Gly Thr Ile Thr Ala Ala Asn Thr Val Thr Val Arg Ser Arg Val Asp 130 135 140 Gly Gln Leu Ile Ala Leu His Phe Gln Glu Gly Gln Gln Val Lys Ala 145 150 155 160 Gly Asp Leu Leu Ala Glu Ile Asp Pro Ser Gln Phe Lys Val Ala Leu 165 170 175 Ala Gln Ala Gln Gly Gln Leu Ala Lys Asp Lys Ala Thr Leu Ala Asn 180 185 190 180 Ala Arg Arg Asp Leu Ala Arg Tyr Gln Gln Leu Ala Lys Thr Asn Leu 195 200 205 Val Ser Arg Gln Glu Leu Asp Ala Gln Gln Ala Leu Val Ser Glu Thr 210 215 220 Glu Gly Thr Ile Lys Ala Asp Glu Ala Ser Val Ala Ser Ala Gln Leu 230 · 235

Gln Leu Asp Trp Ser Arg Ile Thr Ala Pro Val Asp Gly Arg Val Gly 245 250 255 Leu Lys Gln Val Asp Val Gly Asn Gln Ile Ser Ser Gly Asp Thr Thr 260 265 270 Gly Ile Val Val Ile Thr Gln Thr His Pro Ile Asp Leu Val Phe Thr 275 280 285 Leu Pro Glu Ser Asp Ile Ala Thr Val Val Gln Ala Gln Lys Ala Gly 290 295 300 Lys Pro Leu Val Val Glu Ala Trp Asp Arg Thr Asn Ser Lys Leu 305 310 315 320 Ser Glu Gly Thr Leu Leu Ser Leu Asp Asn Gln Ile Asp Ala Thr Thr 325 330 335 Gly Thr Ile Lys Val Lys Ala Arg Phe Asn Asn Gln Asp Asp Ala Leu 340 345 350 Phe Pro Asn Gln Phe Val Asn Ala Arg Met Leu Val Asp Thr Glu Gln 355 360 365 Asn Ala Val Val Ile Pro Thr Ala Ala Leu Gln Met Gly Asn Glu Gly 370 375 380 His Phe Val Trp Val Leu Asn Ser Glu Asn Lys Val Ser Lys His Leu 385 390 395 400 Val Thr Pro Gly Ile Gln Asp Ser Gln Lys Val Val Ile Arg Ala Gly
405 410 415 Ile Ser Ala Gly Asp Arg Val Val Thr Asp Gly Ile Asp Arg Leu Thr 420 425 430Glu Gly Ala Lys Val Glu Val Val Glu Ala Gln Ser Ala Thr Thr Pro 435 440 445 Glu Glu Lys Ala Thr Ser Arg Glu Tyr Ala Lys Lys Gly Ala Arg Ser 455 450 460

<210> 282 <211> 1040 <212> PRT <213> E. Coli

| Add | Secondary | Secondary

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195
                                        200
                                                                     205
Thr Ser Glu Thr Val Arg Thr Ala Ile Thr Gly Ala Asn Val Asn Ser
210 215 220
Ala Lys Gly Ser Leu Asp Gly Pro Ser Arg Ala Val Thr Leu Ser Ala
225 230 235 240
Asn Asp Gln Met Gln Ser Ala Glu Glu Tyr Arg Gln Leu Ile Ile Ala
245 250 255
Tyr Gln Asn Gly Ala Pro Ile Arg Leu Gly Asp Val Ala Thr Val Glu
260 265 270
Gln Gly Ala Glu Asn Ser Trp Leu Gly Ala Trp Ala Asn Lys Glu Gln 275 280 285
Ala Ile Val Met Asn Val Gln Arg Gln Pro Gly Ala Asn Ile Ile Ser
290 295 300
Thr Ala Asp Ser Ile Arg Gln Met Leu Pro Gln Leu Thr Glu Ser Leu 305 310 315 320

Pro Lys Ser Val Lys Val Thr Val Leu Ser Asp Arg Thr Thr Asn Ile 325 330 335
Arg Ala Ser Val Asp Asp Thr Gln Phe Glu Leu Met Met Ala Ile Ala 340 345 350
                                                                       350
Leu Val Val Met Ile Ile Tyr Leu Phe Leu Arg Asn Ile Pro Ala Thr
355 360 365
Ile Ile Pro Gly Val Ala Val Pro Leu Ser Leu Ile Gly Thr Phe Ala 370 375 380
Val Met Val Phe Leu Asp Phe Ser Ile Asn Asn Leu Thr Leu Met Ala
385 390 395 400
Leu Thr Ile Ala Thr Gly Phe Val Val Asp Asp Ala Ile Val Val Ile
405 410 415
Glu Asn Ile Ser Arg Tyr Ile Glu Lys Gly Glu Lys Pro Leu Ala Ala
420 425 430
Ala Leu Lys Gly Ala Gly Glu Ile Gly Phe Thr Île Ile Ser Leu Thr
435 440 445
Phe Ser Leu Ile Ala Val Leu Ile Pro Leu Leu Phe Met Gly Asp Ile 450 455 460
Val Gly Arg Leu Phe Arg Glu Phe Ala Ile Thr Leu Ala Val Ala Ile
465 470 475 480
Leu Ile Ser Ala Val Val Ser Leu Thr Leu Thr Pro Met Met Cys Ala
485 490 495
Arg Met Leu Ser Gln Glu Ser Leu Arg Lys Gln Asn Arg Phe Ser Arg 500 505 510
Ala Ser Glu Lys Met Phe Asp Arg Ile Ile Ala Ala Tyr Gly Arg Gly 515 520 525
Leu Ala Lys Val Leu Asn His Pro Trp Leu Thr Leu Ser Val Ala Leu
530 535 540
Ser Thr Leu Leu Leu Ser Val Leu Leu Trp Val Phe Ile Pro Lys Gly 545 550 555 560
Phe Phe Pro Val Gln Asp Asn Gly Ile Ile Gln Gly Thr Leu Gln Ala
565 570 575
Pro Gln Ser Ser Ser Phe Ala Asn Met Ala Gln Arg Gln Arg Gln Val
Ala Asp Val Ile Leu Gln Asp Pro Ala Val Gln Ser Leu Thr Ser Phe 595 600 605

      Val
      Gly
      Val
      Asp
      Gly
      Thr
      Asn
      Pro
      Ser
      Leu
      Asn
      Ser
      Ala
      Arg
      Leu
      Gln

      610
      615
      620
      620

      Ile
      Asn
      Leu
      Leu
      Asp
      Glu
      Arg
      Asp
      Arg
      Val
      Gln
      Lys
      Val

      625
      630
      635
      640

Ile Ala Arg Leu Gln Thr Ala Val Asp Lys Val Pro Gly Val Asp Leu
645 650 655
Phe Leu Gln Pro Thr Gln Asp Leu Thr Ile Asp Thr Gln Val Ser Arg 660 665 670
Thr Gln Tyr Gln Phe Thr Leu Gln Ala Thr Ser Leu Asp Ala Leu Ser
                                     680
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Thr Trp Val Pro Gln Leu Met Glu Lys Leu Gln Gln Leu Pro Gln Leu
                           695
Ser Asp Val Ser Ser Asp Trp Gln Asp Lys Gly Leu Val Ala Tyr Val 705 710 715 720
Asn Val Asp Arg Asp Ser Ala Ser Arg Leu Gly Ile Ser Met Ala Asp. 725 730 735
Val Asp Asn Ala Leu Tyr Asn Ala Phe Gly Gln Arg Leu Ile Ser Thr
740 745 750
Ile Tyr Thr Gln Ala Asn Gln Tyr Arg Val Val Leu Glu His Asn Thr 755 760 765
Glu Asn Thr Pro Gly Leu Ala Ala Leu Asp Thr Ile Arg Leu Thr Ser
Ser Asp Gly Gly Val Val Pro Leu Ser Ser Ile Ala Lys Ile Glu Gln
785 790 795 800
Arg Phe Ala Pro Leu Ser Ile Asn His Leu Asp Gln Phe Pro Val Thr 805 810 815
Thr Ile Ser Phe Asn Val Pro Asp Asn Tyr Ser Leu Gly Asp Ala Val
820 825 830
Gln Ala Ile Met Asp Thr Glu Lys Thr Leu Asn Leu Pro Val Asp Ile
835 840 845
Thr Thr Gln Phe Gln Gly Ser Thr Leu Ala Phe Gln Ser Ala Leu Gly
850 855 860
Ser Thr Val Trp Leu Ile Val Ala Ala Val Val Ala Met Tyr Ile Val
865 870 875 880
Leu Gly Ile Leu Tyr Glu Ser Phe Ile His Pro Ile Thr Ile Leu Ser
885 890 895
Thr Leu Pro Thr Ala Gly Val Gly Ala Leu Leu Ala Leu Leu Ile Ala 900 905 910
Gly Ser Glu Leu Asp Val Ile Ala Ile Ile Gly Ile Ile Leu Leu Ile
915 920 925
Gly Ile Val Lys Lys Asn Ala Ile Met Met Ile Asp Phe Ala Leu Ala
930 935 940
Ala Glu Arg Glu Gln Gly Met Ser Pro Arg Glu Ala Ile Tyr Gln Ala
945 950 955 960
Cys Leu Leu Arg Phe Arg Pro Ile Leu Met Thr Thr Leu Ala Ala Leu
965 970 975
Leu Gly Ala Leu Pro Leu Met Leu Ser Thr Gly Val Gly Ala Glu Leu 980 985 985 990

Arg Arg Pro Leu Gly Ile Gly Met Val Gly Gly Leu Ile Val Ser Gln 995 1000 1005
Val Leu Thr Leu Phe Thr Thr Pro Val Ile Tyr Leu Leu Phe Asp Arg
  1010 1015
                                                1020
Leu Ala Leu Trp Thr Lys Ser Arg Phe Ala Arg His Glu Glu Glu Ala
                       1030
                                               1035
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<210> 283 <211> 1025 <212> PRT <213> E. Coli

<400> 283

 Met
 Lys
 Phe
 Phe
 Ala
 Leu
 Phe
 Ile
 Tyr
 Arg
 Pro
 Val
 Ala
 Thr
 Ile
 Leu
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 15

 Leu
 Ser
 Val
 Ala
 Ile
 Thr
 Leu
 Cys
 Gly
 Ile
 Leu
 Gly
 Phe
 Arg
 Met
 Leu

 Pro
 Val
 Ala
 Pro
 Cln
 Val
 Asp
 Phe
 Pro
 Val
 Ile
 Ile
 Val
 Ser
 Val
 Ala

 Ala
 Ser
 Leu
 Gly
 Ala
 Ser
 Pro
 Glu
 Thr
 Met
 Ala
 Ser
 Val
 Ala

 Thr
 Pro
 Leu
 Gly
 Arg
 Ile
 Ala
 Gly
 Val
 Ser
 Val
 Ala

 Thr
 Pro
 Leu
 Gly
 Arg
 Ile
 Ala
 Gly
 Val
 Ser
 Ser
 Val
 Ala

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70
                                                  75
Thr Ser Ser Ser Leu Gly Ser Thr Arg Ile Ile Leu Gln Phe Asp
                  85
                                          90
Phe Asp Arg Asp Ile Asn Gly Ala Ala Arg Asp Val Gln Ala Ala Ile
Asn Ala Ala Gln Ser Leu Leu Pro Scr Gly Met Pro Ser Arg Pro Thr
115 120 125
Tyr Arg Lys Ala Asn Pro Ser Asp Ala Pro Ile Met Ile Leu Thr Leu
130 135 140
Thr Ser Asp Thr Tyr Ser Gln Gly Glu Leu Tyr Asp Phe Ala Ser Thr
145 150 155 160
Gln Leu Ala Pro Thr Ile Ser Gln Ile Asp Gly Val Gly Asp Val Asp
165 170 175
Val Gly Gly Ser Ser Leu Pro Ala Val Arg Val Gly Leu Asn Pro Gln
180 185 190

Ala Leu Phe Asn Gln Gly Val Ser Leu Asp Asp Val Arg Thr Ala Val
195 200 205
Ser Asn Ala Asn Val Arg Lys Pro Gln Gly Ala Leu Glu Asp Gly Thr
210 215 220
His Arg Trp Gln Ile Gln Thr Asn Asp Glu Leu Lys Thr Ala Ala Glu
225 230 235 240
Tyr Gln Pro Leu Ile Ile His Tyr Asn Asn Gly Gly Ala Val Arg Leu
245 250 255
Gly Asp Val Ala Thr Val Thr Asp Ser Val Gln Asp Val Arg Asn Ala 260 265 270
Gly Met Thr Asn Ala Lys Pro Ala Ile Leu Leu Met Ile Arg Lys Leu
275 280 285
Pro Glu Ala Asn Ile Ile Gln Thr Val Asp Ser Ile Arg Ala Lys Leu 290 295 300

Pro Glu Leu Gln Glu Thr Ile Pro Ala Ala Ile Asp Leu Gln Ile Ala 305 310 315 320
Gln Asp Arg Ser Pro Thr Ile Arg Ala Ser Leu Glu Glu Val Glu Gln
325 330 335
Thr Leu Ile Ile Ser Val Ala Leu Val Ile Leu Val Val Phe Leu Phe 340 345 350
Leu Arg Ser Gly Arg Ala Thr Ile Ile Pro Ala Val Ser Val Pro Val 355 360 365
Ser Leu Ile Gly Thr Phe Ala Ala Met Tyr Leu Cys Gly Phe Ser Leu
370 375 380
Asn Asn Leu Ser Leu Met Ala Leu Thr Ile Ala Thr Gly Phe Val Val 385 390 395 400
Asp Asp Ala Ile Val Val Leu Glu Asn Ile Ala Arg His Leu Glu Ala
405 410 415
Gly Met Lys Pro Leu Gln Ala Ala Leu Gln Gly Thr Arg Glu Val Gly 420 425 430
Phe Thr Val Leu Ser Met Ser Leu Ser Leu Val Ala Val Phe Leu Pro 435 440 445
Leu Leu Leu Met Gly Gly Leu Pro Gly Arg Leu Leu Arg Glu Phe Ala 450 455 460
Val Thr Leu Ser Val Ala Ile Gly Ile Ser Leu Leu Val Ser Leu Thr
465 470 475 480
Leu Thr Pro Met Met Cys Gly Trp Met Leu Lys Ala Ser Lys Pro Arg
485 490 495
Glu Gln Lys Arg Leu Arg Gly Phe Gly Arg Met Leu Val Ala Leu Gln 500 505 510
Gln Gly Tyr Gly Lys Ser Leu Lys Trp Val Leu Asn His Thr Arg Leu
515 520 525
Val Gly Val Val Leu Leu Gly Thr Ile Ala Leu Asn Ile Trp Leu Tyr
    530
                           535
                                                   540
Ile Ser Ile Pro Lys Thr Phe Phe Pro Glu Gln Asp Thr Gly Val Leu
                        550
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Met Gly Gly Ile Gln Ala Asp Gln Ser Ile Ser Phe Gln Ala Met Arg
                 565
                                       570
Gly Lys Leu Gln Asp Phe Met Lys Ile Ile Arg Asp Asp Pro Ala Val
580 585 590
Asp Asn Val Thr Gly Phe Thr Gly Gly Ser Arg Val Asn Ser Gly Met
595 600 605
Met Phe Ile Thr Leu Lys Pro Arg Asp Glu Arg Ser Glu Thr Ala Gln 610 620
Gln Ile Ile Asp Arg Leu Arg Val Lys Leu Ala Lys Glu Pro Gly Ala
625 630 635 640
Asn Leu Phe Leu Met Ala Val Gln Asp Ile Arg Val Gly Gly Arg Gln 645 650 655
Ser Asn Ala Ser Tyr Gln Tyr Thr Leu Leu Ser Asp Asp Leu Ala Ala 660 665 670
Leu Arg Glu Trp Glu Pro Lys Ile Arg Lys Lys Leu Ala Thr Leu Pro 675 680 685
Glu Leu Ala Asp Val Asn Ser Asp Gln Gln Asp Asn Gly Ala Glu Met
690 695 700
Asn Leu Val Tyr Asp Arg Asp Thr Met Ala Arg Leu Gly Ile Asp Val 705 710 715 720
Gln Ala Ala Asn Ser Leu Leu Asn Asn Ala Phe Gly Gln Arg Gln Ile
725 730 735
Ser Thr Ile Tyr Gln Pro Met Asn Gln Tyr Lys Val Val Met Glu Val 740 745 750
Asp Pro Arg Tyr Thr Gln Asp Ile Ser Ala Leu Glu Lys Met Phe Val 755 760 765
Ile Asn Asn Glu Gly Lys Ala Ile Pro Leu Ser Tyr Phe Ala Lys Trp 770 780
Gln Pro Ala Asn Ala Pro Leu Ser Val Asn His Gln Gly Leu Ser Ala
785 790 795 800
Ala Ser Thr Ile Ser Phe Asn Leu Pro Thr Gly Lys Ser Leu Ser Asp
805 810 815
Ala Ser Ala Ala Ile Asp Arg Ala Met Thr Gln Leu Gly Val Pro Ser
820 825 830
Thr Val Arg Gly Ser Phe Ala Gly Thr Ala Gln Val Phe Gln Glu Thr 835 840 845
Met Asn Ser Gln Val Ile Leu Ile Ile Ala Ala Ile Ala Thr Val Tyr
850 855 860
Ile Val Leu Gly Ile Leu Tyr Glu Ser Tyr Val His Pro Leu Thr Ile
865 870 875 880
Leu Ser Thr Leu Pro Ser Ala Gly Val Gly Ala Leu Leu Ala Leu Glu
885 890 895
Leu Phe Asn Ala Pro Phe Ser Leu Ile Ala Leu Ile Gly Ile Met Leu 900 905 910
Leu Ile Gly Ile Val Lys Lys Asn Ala Ile Met Met Val Asp Phe Ala
915 920 925
Leu Glu Ala Gln Arg His Gly Asn Leu Thr Pro Gln Glu Ala Ile Phe
930 935 940
Gln Ala Cys Leu Leu Arg Phe Arg Pro Ile Met Met Thr Thr Leu Ala
945 950 955 960
Ala Leu Phe Gly Ala Leu Pro Leu Val Leu Ser Gly Gly Asp Gly Ser
965 970 975
Glu Leu Arg Gln Pro Leu Gly Ile Thr Ile Val Gly Gly Leu Val Met
980 985 990
Ser Gln Leu Leu Thr Leu Tyr Thr Thr Pro Val Val Tyr Leu Phe Phe
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                    1000 1005
Asp Arg Leu Arg Leu Arg Phe Ser Arg Lys Pro Lys Gln Thr Val Thr
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    1010
                                                  1020
Glu
1025
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       <213> E. Coli
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Leu Pro Ser Met Ala Gln Ser Leu Gly Glu Ser Pro Leu His Met His 35 40 45
Met Val Ile Val Ser Tyr Val Leu Thr Val Ala Val Met Leu Pro Ala 50 55 60
Ser Gly Trp Leu Ala Asp Lys Val Gly Val Arg Asn Ile Phe Phe Thr 65 70 75 80
Ala Ile Val Leu Phe Thr Leu Gly Ser Leu Phe Cys Ala Leu Ser Gly 85 90 95
Thr Leu Asn Glu Leu Leu Leu Ala Arg Ala Leu Gln Gly Val Gly Gly 100 105 110
Ala Met Met Val Pro Val Gly Arg Leu Thr Val Met Lys Ile Val Pro 115 120 125
       115
Arg Glu Gln Tyr Met Ala Ala Met Thr Phe Val Thr Leu Pro Gly Gln 130 135 140
Val Gly Pro Leu Leu Gly Pro Ala Leu Gly Gly Leu Leu Val Glu Tyr
145 150 155 160
Ala Ser Trp His Trp Ile Phe Leu Ile Asn Ile Pro Val Gly Ile Ile
165 170 175
Gly Ala Ile Ala Thr Leu Leu Met Pro Asn Tyr Thr Met Gln Thr
180 185 190
Arg Arg Phe Asp Leu Ser Gly Phe Leu Leu Leu Ala Val Gly Met Ala 195 200 205
Val Leu Thr Leu Ala Leu Asp Gly Ser Lys Gly Thr Gly Leu Ser Pro
210 215 220
Leu Thr Ile Ala Gly Leu Val Ala Val Gly Val Val Ala Leu Val Leu 225 230 235 240
Tyr Leu Leu His Ala Arg Asn Asn Asn Arg Ala Leu Phe Ser Leu Lys
245 250 255
Leu Phe Arg Thr Arg Thr Phe Ser Leu Gly Leu Ala Gly Ser Phe Ala 260 265 270
Gly Arg Ile Gly Ser Gly Met Leu Pro Phe Met Thr Pro Val Phe Leu
275 280. 285
Gln Ile Gly Leu Gly Phe Ser Pro Phe His Ala Gly Leu Met Met Ile
290 295 300
Pro Met Val Leu Gly Ser Met Gly Met Lys Arg Ile Val Val Gln Val 305 310 315 320
Val Asn Arg Phe Gly Tyr Arg Arg Val Leu Val Ala Thr Thr Leu Gly
325 330 335
Leu Ser Leu Val Thr Leu Leu Phe Met Thr Thr Ala Leu Leu Gly Trp 340 345 350
Tyr Tyr Val Leu Pro Phe Val Leu Phe Leu Gln Gly Met Val Asn Ser 355 360 365
Thr Arg Phe Ser Ser Met Asn Thr Leu Thr Leu Lys Asp Leu Pro Asp 370 375 380
Asn Leu Ala Ser Ser Gly Asn Ser Leu Leu Ser Met Ile Met Gln Leu 385 390 395 400

Ser Met Ser Ile Gly Val Thr Ile Ala Gly Leu Leu Gly Leu Phe 405 410 415
Gly Ser Gln His Val Ser Val Asp Ser Gly Thr Thr Gln Thr Val Phe
             420
                                     425
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 Met
 Tyr
 Thr
 Trp
 Leu
 Ser
 Met
 Ala
 Leu
 Ile
 Ala
 Leu
 Pro
 Ala
 Phe

 435
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<210> 285 <211> 344 <212> PRT <213> E. Coli

<400> 285

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65 70 75 80 Lys Leu Asn Leu His Phe Glu Trp Thr Asn Lys Asn Asn Ile Thr Leu 85 90 95 Ser Asn Asn Gln Thr Ser Phe Thr Ser Gly Tyr Ser Val Thr Val Thr 100 105 110 Pro Ala Ala Ser Asn Ala Lys Val Asn Val Ser Ala Gly Gly Gly 115 120 125 Ser Val Met Ile Asn Gly Val Ala Thr Leu Ser Ser Ala Ser Ser Ser 130 135 140 Asn Ala Gly Val Tyr Ser Phe Asn Leu Thr Leu Ser Tyr Asn Pro Ile 180 185 190 Thr Thr Thr Cys Lys Pro Asp Asp Leu Leu Ile Thr Leu Asp Ser Ile 195 200 205 Pro Val Ser Gln Leu Pro Ala Thr Gly Asn Lys Ala Thr Ile Asn Ser 210 215 220 Lys Gln Gly Asp Ile Ile Leu Arg Cys Lys Asn Leu Leu Gly Gln Gln 225 230 235 240 Asn Gln Thr Ser Arg Lys Met Gln Val Tyr Leu Ser Ser Ser Asp Leu 245 250 255 Leu Thr Asn Ser Asn Thr Ile Leu Lys Gly Ala Glu Asp Asn Gly Val 260 265 270 Gly Phe Ile Leu Glu Ser Asn Gly Ser Pro Val Thr Leu Leu Asn Ile 275 280 285 Thr Asn Ser Ser Lys Gly Tyr Thr Asn Leu Lys Glu Val Ala Ala Lys 290 295 300 Ser Lys Leu Thr Asp Thr Thr Val Ser Ile Pro Ile Thr Ala Ser Tyr 305 310 315 320 Tyr Val Tyr Asp Thr Asn Lys Val Lys Ser Gly Ala Leu Glu Ala Thr 325 330 Ala Leu Ile Asn Val Lys Tyr Asp 340

<210> 286

<211> 826 <212> PRT <213> E. Coli

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50 55 60 Gln Trp Arg Gly Lys Tyr Glu Ile Ile Val Lys Asp Asn Pro Gln Glu 65 70 75 80 Thr Cys Leu Ser Arg Glu Val Ile Lys Arg Leu Gly Ile Asn Ser Asp 85 90 95 Asn Phe Ala Ser Gly Lys Gln Cys Leu Thr Phe Glu Gln Leu Val Gln 100 105 110 Gly Gly Ser Tyr Thr Trp Asp Ile Gly Val Phe Arg Leu Asp Phe Ser 115 120 125 Val Pro Gln Ala Trp Val Glu Glu Leu Glu Ser Gly Tyr Val Pro Pro 130 135 140 Glu Asn Trp Glu Arg Gly Ile Asn Ala Phe Tyr Thr Ser Tyr Tyr Leu 145 150 155 160 Ser Gln Tyr Tyr Ser Asp Tyr Lys Ala Ser Gly Asn Asn Lys Ser Thr 165 170 175 Tyr Val Arg Phe Asn Ser Gly Leu Asn Leu Leu Gly Trp Gln Leu His 180 185 190 Ser Asp Ala Ser Phe Ser Lys Thr Asn Asn Pro Gly Val Trp Lys 195 200 205 Ser Asn Thr Leu Tyr Leu Glu Arg Gly Phe Ala Gln Leu Leu Gly Thr 210 215 220 Leu Arg Val Gly Asp Met Tyr Thr Ser Ser Asp Ile Phe Asp Ser Val 225 230 235 240 Arg Phe Arg Gly Val Arg Leu Phe Arg Asp Met Gln Met Leu Pro Asn 245 250 255 Ser Lys Gln Asn Phe Thr Pro Arg Val Gln Gly Ile Ala Gln Ser Asn 260 265 270 Ala Leu Val Thr Ile Glu Gln Asn Gly Phe Val Val Tyr Gln Lys Glu 275 280 285 Val Pro Pro Gly Pro Phe Ala Ile Thr Asp Leu Gln Leu Ala Gly Gly 290 295 300 Gly Ala Asp Leu Asp Val Ser Val Lys Glu Ala Asp Gly Ser Val Thr 305 310 315 320 Thr Tyr Leu Val Pro Tyr Ala Ala Val Pro Asn Met Leu Gln Pro Gly 325 330 335 Val Ser Lys Tyr Asp Leu Ala Ala Gly Arg Ser His Ile Glu Gly Ala 340 345 350 Ser Lys Gln Ser Asp Phe Val Gln Ala Gly Tyr Gln Tyr Gly Phe Asn 355 360 365 Asn Leu Leu Thr Leu Tyr Gly Gly Ser Met Val Ala Asn Asn Tyr Tyr 370 380

Ala Phe Thr Leu Gly Ala Gly Trp Asn Thr Arg Ile Gly Ala Ile Ser 385

390 395 400 395 Val Asp Ala Thr Lys Ser His Ser Lys Gln Asp Asn Gly Asp Val Phe 405 410 415 Asp Gly Gln Ser Tyr Gln Ile Ala Tyr Asn Lys Phe Val Ser Gln Thr 420 425 430 Ser Thr Arg Phe Gly Leu Ala Ala Trp Arg Tyr Ser Ser Arg Asp Tyr 440

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Arg Thr Phe Asn Asp His Val Trp Ala Asn Asn Lys Asp Asn Tyr Arg
450 455 460
                          455
                                                   460
Arg Asp Glu Asn Asp Val Tyr Asp Ile Ala Asp Tyr Tyr Gln Asn Asp 465 470 475 480
Phe Gly Arg Lys Asn Ser Phe Ser Ala Asn Met Ser Gln Ser Leu Pro
Glu Gly Trp Gly Ser Val Ser Leu Ser Thr Leu Trp Arg Asp Tyr Trp 500 505 510
Gly Arg Ser Gly Ser Ser Lys Asp Tyr Gln Leu Ser Tyr Ser Asn Asn 515 520 525
Leu Arg Arg Ile Ser Tyr Thr Leu Ala Ala Ser Gln Ala Tyr Asp Glu
530 535 540
Asn His His Glu Glu Lys Arg Phe Asn Ile Phe Ile Ser Ile Pro Phe 545 550 555 560
Asp Trp Gly Asp Asp Val Ser Thr Pro Arg Arg Gln Ile Tyr Met Ser
565 570 575
Asn Ser Thr Thr Phe Asp Asp Gln Gly Phe Ala Ser Asn Asn Thr Gly 580 585 590
Leu Ser Gly Thr Val Gly Ser Arg Asp Gln Phe Asn Tyr Gly Val Asn 595 600 605
Leu Ser His Gln His Gln Gly Asn Glu Thr Thr Ala Gly Ala Asn Leu 610 615 620
Thr Trp Asn Ala Pro Val Ala Thr Val Asn Gly Ser Tyr Ser Gln Ser 625 630 635 640
Ser Thr Tyr Arg Gln Ala Gly Ala Ser Val Ser Gly Gly Ile Val Ala
645 650 655
Trp Ser Gly Gly Val Asn Leu Ala Asn Arg Leu Ser Glu Thr Phe Ala 660 665 670
Val Met Asn Ala Pro Gly Ile Lys Asp Ala Tyr Val Asn Gly Gln Lys 675 680 685
Tyr Arg Thr Thr Asn Arg Asn Gly Val Val Ile Tyr Asp Gly Met Thr
690 695 700
Pro Tyr Arg Glu Asn His Leu Met Leu Asp Val Ser Gln Ser Asp Ser 705 710 715 720
Glu Ala Glu Leu Arg Gly Asn Arg Lys Ile Ala Ala Pro Tyr Arg Gly
725 730 735
Ala Val Val Leu Val Asn Phe Asp Thr Asp Gln Arg Lys Pro Trp Phe 740 745 750
Ile Lys Ala Leu Arg Ala Asp Gly Gln Ser Leu Thr Phe Gly Tyr Glu 755 760 765
Val Asn Asp Ile His Gly His Asn Ile Gly Val Val Gly Gln Gly Ser
770 775 780
Gln Leu Phe Ile Arg Thr Asn Glu Val Pro Pro Ser Val Asn Val Ala
785 790 795 800
Ile Asp Lys Gln Gln Gly Leu Ser Cys Thr Ile Thr Phe Gly Lys Glu
805 810 815
Ile Asp Glu Ser Arg Asn Tyr Ile Cys Gln
              820
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<210> 287 <211> 239 <212> PRT <213> E. Coli

<400> 287

 Met Ala Ala Ile Pro Trp Arg Pro Phe Asn Leu Arg Gly Ile Lys Met

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 10
 15

 Lys Gly Leu Leu Ser Leu Leu Ile Phe Ser Met Val Leu Pro Ala His
 20
 25
 30

 Ala Gly Ile Val Ile Tyr Gly Thr Arg Ile Ile Tyr Pro Ala Glu Asn

 Lys
 Glu
 Val
 Met
 Val
 Gln
 Leu
 Met
 Asn
 Gln
 Gln
 Asn
 And
 Arg
 Ser
 Ser
 Leu

 Leu
 Gln
 Ala
 Trp
 Ile
 Asp
 Gly
 Asp
 Thr
 Ser
 Leu
 Pro
 Pro
 Glu
 Lys
 Bol
 Asp
 Thr
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 Fro
 Leu
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 Lys
 Bol
 Asp
 Fro
 Pro
 Pro
 Pro
 Glu
 Lys
 Ala
 Bol
 Asp
 Fro
 Pro
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<210> 288 <211> 180 <212> PRT <213> E. Coli

<400> 288

 Met
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 Arg
 Ser
 Ile
 Ile
 Ala
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 Phe
 Met

 Ser
 Ala
 Gly
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 Phe
 Ala
 Ala
 Asp
 Val
 Asp
 Thr
 Leu
 Thr
 Leu
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 Ile
 July
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 Phe
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 Asp
 Asp
 Thr
 Ser
 Thr
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 Asp
 Asp
 Asp
 Phe
 Glu
 Asp
 Asp

<210> 289

<211> 112 <212> PRT <213> E. Coli

 400> 289

 Met Ser Ser Glu Arg Asp Leu Val Asn Phe Leu Gly Asp Phe Ser Met 1
 5
 10
 15
 15

 Asp Val Ala Lys Ala Val Ile Ala Gly Gly Val Ala Thr Ala Ile Gly 20
 25
 30

 Ser Leu Ala Ser Phe Ala Cys Val Ser Phe Gly Phe Pro Val Ile Leu 45

 Val Gly Gly Ala Ile Leu Leu Thr Gly Ile Val Cys Thr Val Val Leu 50

 Asn Glu Ile Asp Ala Gln Cys His Leu Ser Glu Lys Leu Lys Tyr Ala 65

 Glu Asn Met Thr Pro Phe Met Tyr Val Leu Asn Thr Pro Pro Val Ile 100

<210> 290 <211> 193 <212> PRT <213> E. Coli

<400> 290 Met Thr Asp Tyr Leu Leu Phe Val Gly Thr Val Leu Val Asn Asn 1 5 10 15 Phe Val Leu Val Lys Phe Leu Gly Leu Cys Pro Phe Met Gly Val Ser 20 25 30 Lys Lys Leu Glu Thr Ala Met Gly Met Gly Leu Ala Thr Thr Phe Val 35 40 45 Met Thr Leu Ala Ser Ile Cys Ala Trp Leu Ile Asp Thr Trp Ile Leu 50 55 60 Ile Pro Leu Asn Leu Ile Tyr Leu Arg Thr Leu Ala Phe Ile Leu Val 65 70 75 80 Ile Ala Val Val Gln Phe Thr Glu Met Val Val Arg Lys Thr Ser 85 90 95 Pro Val Leu Tyr Arg Leu Leu Gly Ile Phe Leu Pro Leu Ile Thr Thr Asn Cys Ala Val Leu Gly Val Ala Leu Leu Asn Ile Asn Leu Gly His 115 120 125 Asn Phe Leu Gln Ser Ala Leu Tyr Gly Phe Ser Ala Ala Val Gly Phe 130 135 140 Ser Leu Val Met Val Leu Phe Ala Ala Ile Arg Glu Arg Leu Ala Val 145 150 155 160 Ala Asp Val Pro Ala Pro Phe Arg Gly Asn Ala Ile Ala Leu Ile Thr 165 170 175 170 175 Ala Gly Leu Met Ser Leu Ala Phe Met Gly Phc Ser Gly Leu Val Lys 180 190

<210> 291 <211> 192 <212> PRT <213> E. Coli

<400> 291 Met Asn Ala Ile Trp Ile Ala Val Ala Val Ser Leu Leu Gly Leu 10 Ala Phe Gly Ala Ile Leu Gly Tyr Ala Ser Arg Arg Phe Ala Val Glu 20 25 30 Asp Asp Pro Val Val Glu Lys Ile Asp Glu Ile Leu Pro Gln Ser Gln 35 40 45 Cys Gly Gln Cys Gly Tyr Pro Gly Cys Arg Pro Tyr Ala Glu Ala Ile 50 55 60 Ser Cys Asn Gly Glu Lys Ile Asn Arg Cys Ala Pro Gly Gly Glu Ala 65 70 75 80 Val Met Leu Lys Ile Ala Glu Leu Leu Asn Val Glu Pro Gln Pro Leu 85 90 95 Asp Gly Glu Ala Glu Glu Ile Thr Pro Ala Arg Met Val Ala Val Ile 100 105 110 Asp Glu Asn Asn Cys Ile Gly Cys Thr Lys Cys Ile Gln Ala Cys Pro 115 120 125 Val Asp Ala Ile Val Gly Ala Thr Arg Ala Met His Thr Val Met Ser 130 135 140 Asp Leu Cys Thr Gly Cys Asn Leu Cys Val Asp Pro Cys Pro Thr His 145 150 155 160 Cys Ile Ser Leu Gln Pro Val Ala Glu Thr Pro Asp Ser Trp Lys Trp 165 170 175 Asp Leu Asn Thr Ile Pro Val Arg Ile Ile Pro Val Glu His His Ala 180 185

<210> 292 <211> 740 <212> PRT <213> E. Coli

Arg Ala Val Leu Ala Asp Ser Asn Asp Ile Ser Leu Arg Val Ile Pro 230 235 Thr Lys Tyr Pro Ser Gly Gly Ala Lys Gln Leu Thr Tyr Ile Leu Thr 245 250 255 Gly Lys Gln Val Pro His Gly Gly Arg Ser Ser Asp Ile Gly Val Leu 260 265 270 Met Gln Asn Val Gly Thr Ala Tyr Ala Val Lys Arg Ala Val Ile Asp 275 280 285 Gly Glu Pro Ile Thr Glu Arg Val Val Thr Leu Thr Gly Glu Ala Ile 290 295 300 Ala Arg Pro Gly Asn Val Trp Ala Arg Leu Gly Thr Pro Val Arg His 305 310 315 320 Leu Leu Asn Asp Ala Gly Phe Cys Pro Ser Ala Asp Gln Met Val Ile 325 330 335 Met Gly Gly Pro Leu Met Gly Phe Thr Leu Pro Trp Leu Asp Val Pro 340 345 350 Val Val Lys Ile Thr Asn Cys Leu Leu Ala Pro Ser Ala Asn Glu Leu 355 360 365 Gly Glu Pro Gln Glu Glu Gln Ser Cys Ile Arg Cys Ser Ala Cys Ala 370 375 380 Asp Ala Cys Pro Ala Asp Leu Leu Pro Gln Gln Leu Tyr Trp Phe Ser 385 390 395 400 Lys Gly Gln Gln His Asp Lys Ala Thr Thr His Asn Ile Ala Asp Cys
405
410
415

Ile Glu Cys Gly Ala Cys Ala Trp Val Cys Pro Ser Asn Ile Pro Leu
420
425
430 Val Gln Tyr Phe Arg Gln Glu Lys Ala Glu Ile Ala Ala Ile Arg Gln 435 440 445 Glu Glu Lys Arg Ala Ala Glu Ala Lys Ala Arg Phe Glu Ala Arg Gln 450 455 460 Ala Arg Leu Glu Arg Glu Lys Ala Ala Arg Leu Glu Arg His Lys Ser 465 470 475 480 Ala Ala Val Gln Pro Ala Ala Lys Asp Lys Asp Ala Ile Ala Ala 485 490 495 Leu Ala Arg Val Lys Glu Lys Gln Ala Gln Ala Thr Gln Pro Ile Val 500 505 510 Ile Lys Ala Gly Glu Arg Pro Asp Asn Ser Ala Ile Ile Ala Ala Arg 515 520 525 Glu Ala Arg Lys Ala Gln Ala Arg Ala Lys Gln Ala Glu Leu Gln Gln 530 535 540 Thr Asn Asp Ala Ala Thr Val Ala Asp Pro Arg Lys Thr Ala Val Glu 545 550 555 560 Ala Ala Ile Ala Arg Ala Lys Ala Arg Lys Leu Glu Gln Gln Gln Ala 565 570 575 Asn Ala Glu Pro Glu Gln Gln Val Asp Pro Arg Lys Ala Ala Val Glu 580 585 590 Ala Ala Ile Ala Arg Ala Lys Ala Arg Lys Leu Glu Gln Gln Gln Ala 595 600 605 Asn Ala Glu Pro Glu Glu Gln Val Asp Pro Arg Lys Ala Ala Val Glu 610 615 620 Ala Ala Ile Ala Arg Ala Lys Ala Arg Lys Leu Glu Gln Gln Ala 625 630 635 640 Asn Ala Glu Pro Glu Gln Gln Val Asp Pro Arg Lys Ala Ala Val Glu 645 650 655 Ala Ala Ile Ala Arg Ala Lys Ala Arg Lys Arg Glu Gln Gln Pro Ala 660 665 670 Asn Ala Glu Pro Glu Glu Gln Val Asp Pro Arg Lys Ala Ala Val Glu 675 680 685 Ala Ala Ile Ala Arg Ala Lys Ala Arg Lys Leu Glu Gln Gln Gln Ala 690 695 700 Asn Ala Val Pro Glu Glu Gln Val Asp Pro Arg Lys Ala Ala Val Ala

705 710 715 720
Ala Ala Ile Ala Arg Ala Gln Ala Lys Lys Ala Ala Gln Gln Lys Val
735
Val Asn Glu Asp
740

<210> 293 <211> 352 <212> PRT <213> E. Coli

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<210> 294

<211> 206 <212> PRT <213> E. Coli

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<210> 295 <211> 231 <212> PRT <213> E. Coli

<210> 296 <211> 211 <212> PRT <213> E. Coli

<400> 296 Met Asn Lys Ala Lys Arg Leu Glu Ile Leu Thr Arg Leu Arg Glu Asn 1 5 10 15 Asn Pro His Pro Thr Thr Glu Leu Asn Phe Ser Ser Pro Phe Glu Leu 20 25 30 Leu Ile Ala Val Leu Leu Ser Ala Gln Ala Thr Asp Val Ser Val Asn 35 40 45 Lys Ala Thr Ala Lys Leu Tyr Pro Val Ala Asn Thr Pro Ala Ala Met 50 60 Leu Glu Leu Gly Val Glu Gly Val Lys Thr Tyr Ile Lys Thr Ile Gly 65 70 75 80 Leu Tyr Asn Ser Lys Ala Glu Asn Ile Ile Lys Thr Cys Arg Ile Leu 85 90 95 Leu Glu Gln His Asn Gly Glu Val Pro Glu Asp Arg Ala Ala Leu Glu 100 105 110 Ala Leu Pro Gly Val Gly Arg Lys Thr Ala Asn Val Val Leu Asn Thr 115 120 125 Ala Phe Gly Trp Pro Thr Ile Ala Val Asp Thr His Ile Phe Arg Val 130 135 140 Cys Asn Arg Thr Gln Phe Ala Pro Gly Lys Asn Val Glu Gln Val Glu 145 150 155 160 Glu Lys Leu Leu Lys Val Val Pro Ala Glu Phe Lys Val Asp Cys His 165 . 170 175 His Trp Leu Ile Leu His Gly Arg Tyr Thr Cys Ile Ala Arg Lys Pro 180 185 190 185 190 Arg Cys Gly Ser Cys Ile Ile Glu Asp Leu Cys Glu Tyr Lys Glu Lys 195 200 Val Asp Ile

<210> 297 <211> 167 <212> PRT <213> E. Coli

210

<210> 298 <211> 176 <212> PRT <213> E. Coli

<400> 298

 Met
 Lys
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 Asn
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 Ile
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 Cys
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 Gly
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 Gly
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 Thr
 Ile
 Ile
 Ile
 Leu
 Gly
 Leu
 Asn
 Ile
 Ile
 Leu
 Ser
 Gly
 Arg
 Arg
 Ser
 Val
 Ile
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 Arg
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<210> 299 <211> 382 <212> PRT <213> E. Coli

Gln Ile Ser Phe Gly Leu Asn Val Pro Phe Gly Asp Ile Thr Thr Ser 65 70 75 80 Leu Asn Tyr Ser Tyr Ser Asn Asn Ile Trp Gln Asn Asp Arg Asp His 85 90 95 Leu Leu Ala Phe Thr Leu Asn Val Pro Phe Ser His Trp Met Arg Thr 100 105 110 Asp Ser Gln Ser Ala Phe Arg Asn Ser Asn Ala Ser Tyr Ser Met Ser 115 120 125 Asn Asp Leu Lys Gly Gly Met Thr Asn Leu Ser Gly Val Tyr Gly Thr 130 135 140 Leu Leu Pro Asp Asn Asn Leu Asn Tyr Ser Val Gln Val Gly Asn Thr 145 150 150 160 His Gly Gly Asn Thr Ser Ser Gly Thr Ser Gly Tyr Ser Ser Leu Asn 165 170 175 Tyr Arg Gly Ala Tyr Gly Asn Thr Asn Val Gly Tyr Ser Arg Ser Gly 180 185 190 Asp Ser Ser Gln Ile Tyr Tyr Gly Met Ser Gly Gly Ile Ile Ala His 195 200 205 Ala Asp Gly Ile Thr Phe Gly Gln Pro Leu Gly Asp Thr Met Val Leu 210 215 220 Val Lys Ala Pro Gly Ala Asp Asn Val Lys Ile Glu Asn Gln Thr Gly 225 230 235 240 Ile His Thr Asp Trp Arg Gly Tyr Ala Ile Leu Pro Phe Ala Thr Glu 245 250 255 Tyr Arg Glu Asn Arg Val Ala Leu Asn Ala Asn Ser Leu Ala Asp Asn 260 265 270 Val Glu Leu Asp Glu Thr Val Val Thr Val Ile Pro Thr His Gly Ala 275 280 285 Ile Ala Arg Ala Thr Phe Asn Ala Gln Ile Gly Gly Lys Val Leu Met 290 295 300 Thr Leu Lys Tyr Gly Asn Lys Ser Val Pro Phe Gly Ala Ile Val Thr 305 310 315 320 His Gly Glu Asn Lys Asn Gly Ser Ile Val Ala Glu Asn Gly Gln Val 325 330 335 Tyr Leu Thr Gly Leu Pro Gln Ser Gly Gln Leu Gln Val Ser Trp Gly 340 345 350 Lys Asp Lys Asn Ser Asn Cys Ile Val Glu Tyr Lys Leu Pro Glu Val 355 . 360 365 Ser Pro Gly Thr Leu Leu Asn Gln Gln Thr Ala Ile Cys Arg

<210> 300 <211> 138 <212> PRT <213> E. Coli

<400> 300

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 Val Ala Pro Phe Leu Ala Gly Ile Gln Asn Glu Glu Gln Tyr Thr Gln 20
 25
 30

 Ala Leu Glu Leu Val Asp His Leu Leu Leu Asn Asp Pro Glu Asn Pro 35
 40
 40

 Leu Leu Asp Leu Val Cys Ala Lys Ile Thr Ala Trp Glu Glu Ser Ala 50
 55
 60

 Pro Glu Phe Ala Glu Phe Asn Ala Met Ala Gln Ala Met Pro Gly Gly 70
 75
 80

 65
 70
 90
 95

 Asp Leu Pro Glu Ile Gly Ser Lys Ser Met Val Ser Arg Val Leu Ser

100 105 110

Gly Lys Arg Lys Leu Thr Leu Glu His Ala Lys Lys Leu Ala Thr Arg
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Phe Gly Ile Ser Pro Ala Leu Phe Ile Asp
130 135

<210> 301 <211> 104 <212> PRT <213> E. Coli

<210> 302 <211> 2383 <212> PRT <213> E. Coli

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Lys Asn Ser Gln Phe Asp Phe Leu His Pro Trp Tyr Glu Thr Pro Asp 225 230 230 235 240
Asn Leu Phe Phe Ser Gln His Thr Leu His Arg Thr Asp Glu Arg Thr 245 250 255
Gln Ile Asn Asn Gly Leu Gly Trp Arg His Phe Thr Pro Thr Trp Met 260 265 270
Ser Gly Ile Asn Phe Phe Phe Asp His Asp Leu Ser Arg Tyr His Ser
275 280 285
Arg Ala Gly Ile Gly Ala Glu Tyr Trp Arg Asp Tyr Leu Lys Leu Ser
290 295 300
Ser Asn Gly Tyr Leu Arg Leu Thr Asn Trp Arg Ser Ala Pro Glu Leu
305 310 315 320
Asp Asn Asp Tyr Glu Ala Arg Pro Ala Asn Gly Trp Asp Val Arg Ala
325 330 335
Glu Ser Trp Leu Pro Ala Trp Pro His Leu Gly Gly Lys Leu Val Tyr 340 345 350
Glu Gln Tyr Tyr Gly Asp Glu Val Ala Leu Phe Asp Lys Asp Asp Arg
355 360 365
Gln Ser Asn Pro His Ala Ile Thr Ala Gly Leu Asn Tyr Thr Pro Phe
370 375 380
Pro Leu Met Thr Phe Ser Ala Glu Gln Arg Gln Gly Lys Gln Gly Glu
385 390 395 400
Asn Asp Thr Arg Phe Ala Val Asp Phe Thr Trp Gln Pro Gly Ser Ala
405 410 415
Met Gln Lys Gln Leu Asp Pro Asn Glu Val Ala Ala Arg Arg Ser Leu
420 425 430
Ala Gly Ser Arg Tyr Asp Leu Val Asp Arg Asn Asn Asn Ile Val Leu
435 440 445
Glu Tyr Arg Lys Lys Glu Leu Val Arg Leu Thr Leu Thr Asp Pro Val
450 455 460
Thr Gly Lys Ser Gly Glu Val Lys Ser Leu Val Ser Ser Leu Gln Thr
465 470 475 480
Lys Tyr Ala Leu Lys Gly Tyr Asn Val Glu Ala Thr Ala Leu Glu Ala
485 490 495
Ala Gly Gly Lys Val Val Thr Thr Gly Lys Asp Ile Leu Val Thr Leu
500 505 510
Pro Ala Tyr Arg Phe Thr Ser Thr Pro Glu Thr Asp Asn Thr Trp Pro 515 520 525
Ile Glu Val Thr Ala Glu Asp Val Lys Gly Asn Leu Ser Asn Arg Glu
530 535 . 540
Gln Ser Met Val Val Val Gln Ala Pro Thr Leu Ser Gln Lys Asp Ser 545 550 555 560
Ser Val Ser Leu Ser Thr Gln Thr Leu Asn Ala Asp Ser His Ser Thr
565 570 575
Ala Thr Leu Thr Phe Ile Ala His Asp Ala Ala Gly Asn Pro Val Val 580 585 590
Gly Leu Val Leu Ser Thr Arg His Glu Gly Val Gln Asp Ile Thr Leu 595 600 605
Ser Asp Trp Lys Asp Asn Gly Asp Gly Ser Tyr Thr Gln Ile Leu Thr 610 620
Thr Gly Ala Met Ser Gly Thr Leu Thr Leu Met Pro Gln Leu Asn Gly 625 630 635 640
Val Asp Ala Ala Lys Ala Pro Ala Val Val Asn Ile Ile Ser Val Ser
645 650 655
Ser Ser Arg Thr His Ser Ser Ile Lys Ile Asp Lys Asp Arg Tyr Leu 660 665 670
Ser Gly Asn Pro Ile Glu Val Thr Val Glu Leu Arg Asp Glu Asn Asp
                                 680
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Lys Pro Val Lys Glu Gln Lys Gln Gln Leu Asn Asn Ala Val Ser Ile 690 695 700 695 700 690 Asp Asn Val Lys Pro Gly Val Thr Thr Asp Trp Lys Glu Thr Ala Asp 705 710 715 720 .Gly Val Tyr Lys Ala Thr Tyr Thr Ala Tyr Thr Lys Gly Ser Gly Leu 725 730 735 Thr Ala Lys Leu Met Gln Asn Trp Asn Glu Asp Leu His Thr Ala 740 745 750Gly Phe Ile Ile Asp Ala Asn Pro Gln Ser Ala Lys Ile Ala Thr Leu 755 760 765 Ser Ala Ser Asn Asn Gly Val Leu Ala Asn Glu Asn Ala Ala Asn Thr 770 775 780 Val Ser Val Asn Val Ala Asp Glu Gly Ser Asn Pro Ile Asn Asp His 785 790 795 800 Thr Val Thr Phe Ala Val Leu Ser Gly Ser Ala Thr Ser Phe Asn Asn 805 810 915 Gln Asn Thr Ala Lys Thr Asp Val Asn Gly Leu Ala Thr Phe Asp Leu 820 825 830 820 Lys Ser Ser Lys Gln Glu Asp Asn Thr Val Glu Val Thr Leu Glu Asn 835 840 845 Gly Val Lys Gln Thr Leu Ile Val Ser Phe Val Gly Asp Ser Ser Thr 850 855 860 Ala Gln Val Asp Leu Gln Lys Ser Lys Asn Glu Val Val Ala Asp Gly 865 870 875 880 Asn Asp Ser Val Thr Met Thr Ala Thr Val Arg Asp Ala Lys Gly Asn 885 890 895 Leu Leu Asn Asp Val Met Val Thr Phe Asn Val Asn Ser Ala Glu Ala 900 905 910 Lys Leu Ser Gln Thr Glu Val Asn Ser His Asp Gly Ile Ala Thr Ala
915 920 925

Thr Leu Thr Ser Leu Lys Asn Gly Asp Tyr Arg Val Thr Ala Ser Val
930 935 940 Ser Ser Gly Ser Gln Ala Asn Gln Gln Val Asn Phe Ile Gly Asp Gln 945 950 955 960 Ser Thr Ala Ala Leu Thr Leu Ser Val Pro Ser Gly Asp Ile Thr Val 965 970 975 Thr Asn Thr Ala Pro Gln Tyr Met Thr Ala Thr Leu Gln Asp Lys Asn 980 985 990 Gly Asn Pro Leu Lys Asp Lys Glu Ile Thr Phe Ser Val Pro Asn Asp 995 1000 1005 Val Ala Ser Lys Phe Ser Ile Ser Asn Gly Gly Lys Gly Met Thr Asp 1010 1015 1020 Ser Asn Gly Val Ala Ile Ala Ser Leu Thr Gly Thr Leu Ala Gly Thr 1025 1030 1035 1046
His Met Ile Met Ala Arg Leu Ala Asn Ser Asn Val Ser Asp Ala Gln 1045 1050 1055 1040 Pro Met Thr Phe Val Ala Asp Lys Asp Arg Ala Val Val Leu Gln 1060 1065 1070 Thr Ser Lys Ala Glu Ile Ile Gly Asn Gly Val Asp Glu Thr Thr Leu 1075 1080 1085 Thr Ala Thr Val Lys Asp Pro Ser Asn His Pro Val Ala Gly Ile Thr 1090 1095 1100 Val Asn Phe Thr Met Pro Gln Asp Val Ala Ala Asn Phe Thr Leu Glu 1105 1110 1115 1120 Asn Asn Gly Ile Ala Ile Thr Gln Ala Asn Gly Glu Ala His Val Thr 1125 1130 1135

Leu Lys Gly Lys Lys Ala Gly Thr His Thr Val Thr Ala Thr Leu Gly 1140 1145 1150 Asn Asn Asn Thr Ser Asp Ser Gln Pro Val Thr Phe Val Ala Asp Lys 1155 1160 1165 Ala Ser Ala Gln Val Val Leu Gln Ile Ser Lys Asp Glu Ile Thr Gly

1175 1180 Asn Gly Val Asp Ser Ala Thr Leu Thr Ala Thr Val Lys Asp Gln Phe 1185 1190 1195 120 1200 Asp Asn Glu Val Asn Asn Leu Pro Val Thr Phe Ser Ser Ala Ser Ser 1205 1210 1215 Gly Leu Thr Leu Thr Pro Gly Val Ser Asn Thr Asn Glu Ser Gly Ile 1220 1225 1230 Ala Gln Ala Thr Leu Ala Gly Val Ala Phe Gly Glu Lys Thr Val Thr 1235 1240 1245 Ala Ser Leu Ala Asn Asn Gly Ala Ser Asp Asn Lys Thr Val His Phe 1250 1255 1260 Ile Gly Asp Thr Ala Ala Ala Lys Ile Ile Glu Leu Ala Pro Val Pro 1265 1270 1275 128 1280 Asp Ser Ile Ile Ala Gly Thr Pro Gln Asn Ser Ser Gly Ser Val Ile
1285 1290 1295

Thr Ala Thr Val Val Asp Asn Asn Gly Phe Pro Val Lys Gly Val Thr
1300 1305 1310 Val Asn Phe Thr Ser Asn Ala Ala Thr Ala Glu Met Thr Asn Gly Gly 1315 1320 1325 Gln Ala Val Thr Asn Glu Gln Gly Lys Ala Thr Val Thr Tyr Thr Asn 1330 1335 1340 Thr Arg Ser Ser Ile Glu Ser Gly Ala Arg Pro Asp Thr Val Glu Ala 1345 1350 1355 136 1360 Ser Leu Glu Asn Gly Ser Ser Thr Leu Ser Thr Ser Ile Asn Val Asn 1365 1370 1375 Ala Asp Ala Ser Thr Ala His Leu Thr Leu Leu Gln Ala Leu Phe Asp 1380 1385 1390 Thr Val Ser Ala Gly Glu Thr Thr Ser Leu Tyr Ile Glu Val Lys Asp 1395 1400 1405 Asn Tyr Gly Asn Gly Val Pro Gln Gln Glu Val Thr Leu Ser Val Ser 1410 1415 Pro Ser Glu Gly Val Thr Pro Ser Asn Asn Ala Ile Tyr Thr Thr Asn 1430 1435 1440 His Asp Gly Asn Phe Tyr Ala Ser Phe Thr Ala Thr Lys Ala Gly Val 1445 1450 1455 Tyr Gln Leu Thr Ala Thr Leu Glu Asn Gly Asp Ser Met Gln Gln Thr 1460 1465 1470 Val Thr Tyr Val Pro Asn Val Ala Asn Ala Glu Ile Thr Leu Ala Ala 1475 1480 1485 1475 1480 1485

Ser Lys Asp Pro Val Ile Ala Asp Asn Asn Asp Leu Thr Thr Leu Thr
1490 1495 1500

Ala Thr Val Ala Asp Thr Glu Gly Asn Ala Ile Ala Asn Thr Glu Val
1505 1510 1515 1520

Thr Phe Thr Leu Pro Glu Asp Val Lys Ala Asn Phe Thr Leu Ser Asp
1525 1530 1535

Gly Gly Lys Val Ile Thr Asp Ala Glu Gly Lys Ala Lys Val Thr Leu
1540 1550

Luc Gly Thr Lye Ala Gly Ala His Thr Val Thr Ala Ser Met Thr Gly 1520 Lys Gly Thr Lys Ala Gly Ala His Thr Val Thr Ala Ser Met Thr Gly 1555 1560 1565 Gly Lys Ser Glu Gln Leu Val Val Asn Phe Ile Ala Asp Thr Leu Thr 1570 1575 1580 Ala Gln Val Asn Leu Asn Val Thr Glu Asp Asn Phe Ile Ala Asn Asn 1585 1590 1595 1600 1600 Val Gly Met Thr Arg Leu Gln Ala Thr Val Thr Asp Gly Asn Gly Asn 1605 1610 1615 Pro Leu Ala Asn Glu Ala Val Thr Phe Thr Leu Pro Ala Asp Val Ser 1620 1625 1630 Ala Ser Phe Thr Leu Gly Gln Gly Gly Ser Ala Ile Thr Asp Ile Asn 1635 1640 1645 Gly Lys Ala Glu Val Thr Leu Ser Gly Thr Lys Ser Gly Thr Tyr Pro 1650 1655 1660

Val Thr Val Ser Val Asn Asn Tyr Gly Val Ser Asp Thr Lys Gln Val 1665 1670 1675 Thr Leu Ile Ala Asp Ala Gly Thr Ala Lys Leu Ala Ser Leu Thr Ser 1685 1690 1695 1695 Val Tyr Ser Phe Val Val Ser Thr Thr Glu Gly Ala Thr Met Thr Ala 1700 1705 1710 Ser Val Thr Asp Ala Asn Gly Asn Pro Val Glu Gly Ile Lys Val Asn 1715 1720 1725

Phe Arg Gly Thr Ser Val Thr Leu Ser Ser Thr Ser Val Glu Thr Asp 1730 1735 Asp Arg Gly Phe Ala Glu Ile Leu Val Thr Ser Thr Glu Val Gly Leu 1745 1750 1755 1766 1760 Lys Thr Val Ser Ala Ser Leu Ala Asp Lys Pro Thr Glu Val Ile Ser Arg Leu Leu Asn Ala Ser Ala Asp Val Asn Ser Ala Thr Ile Thr Ser 1780 1785 1790 Leu Glu Ile Pro Glu Gly Gln Val Met Val Ala Gln Asp Val Ala Val 1795 1800 1805 Lys Ala His Val Asn Asp Gln Phe Gly Asn Pro Val Ala His Gln Pro 1810 1825 1820

Val Thr Phe Ser Ala Glu Pro Ser Ser Gln Met Ile Ile Ser Gln Asn 1825 1830 1835 1840 Thr Val Ser Thr Asn Thr Gln Gly Val Ala Glu Val Thr Met Thr Pro 1845 1850 1855 Glu Arg Asn Gly Ser Tyr Met Val Lys Ala Ser Leu Pro Asn Gly Ala 1860 1865 1870 Ser Leu Glu Lys Gln Leu Glu Ala Ile Asp Glu Lys Leu Thr Leu Thr 1875 1880 1885 Ala Ser Ser Pro Leu Ile Gly Val Tyr Ala Pro Thr Gly Ala Thr Leu 1890 1895 1900 Thr Ala Thr Leu Thr Ser Ala Asn Gly Thr Pro Val Glu Gly Gln Val 1905 1910 1915 192 1920 Ile Asn Phe Ser Val Thr Pro Glu Gly Ala Thr Leu Ser Gly Gly Lys 1925 1930 1935 Val Arg Thr Asn Ser Ser Gly Gln Ala Pro Val Val Leu Thr Ser Asn 1940 1945 1950 Lys Val Gly Thr Tyr Thr Val Thr Ala Ser Phe His Asn Gly Val Thr 1955 1960 1965 Ile Gin Thr Gin Thr Thr Val Lys Val Thr Gly Asn Ser Ser Thr Ala 1970 1975 1980 His Val Ala Ser Phe Ile Ala Asp Pro Ser Thr Ile Ala Ala Thr Asn 1985 1990 1995 200 2000 Thr Asp Leu Ser Thr Leu Lys Ala Thr Val Glu Asp Gly Ser Gly Asn 2005 2010 2015 Leu Ile Glu Gly Leu Thr Val Tyr Phe Ala Leu Lys Ser Gly Ser Ala 2020 2025 2030 Thr Leu Thr Ser Leu Thr Ala Val Thr Asp Gln Asn Gly Ile Ala Thr 2035 2040 2045

Thr Ser Val Lys Gly Ala Met Thr Gly Ser Val Thr Val Ser Ala Val 2055 2060 2050 Thr Thr Ala Gly Gly Met Gln Thr Val Asp Ile Thr Leu Val Ala Gly 2065 2070 2075 208 2080 Pro Ala Asp Thr Ser Gln Ser Val Leu Lys Ser Asn Arg Ser Ser Leu 2085 2090 2095 Lys Gly Asp Tyr Thr Asp Ser Ala Glu Leu Arg Leu Val Leu His Asp 2100 2105 2110 Ile Ser Gly Asn Pro Ile Lys Val Ser Glu Gly Met Glu Phe Val Gln 2115 2120 2125 Ser Gly Thr Asn Val Pro Tyr Ile Lys Ile Ser Ala Ile Asp Tyr Ser 2135 2140 2130 Leu Asn Ile Asn Gly Asp Tyr Lys Ala Thr Val Thr Gly Gly Glu

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2150
                                               2155
Gly Ile Ala Thr Leu Ile Pro Val Leu Asn Gly Val His Gln Ala Gly 2165 2170 2175
Leu Ser Thr Thr Ile Gln Phe Thr Arg Ala Glu Asp Lys Ile Met Ser
2180 2185 2190
Gly Thr Val Ser Val Asn Gly Thr Asp Leu Pro Thr Thr Thr Phe Pro
2195 2200 2205
Ser Gln Gly Phe Thr Gly Ala Tyr Tyr Gln Leu Asn Asn Asp Asn Phe
2210 2215 2220
Ala Pro Gly Lys Thr Ala Ala Asp Tyr Glu Phe Ser Ser Ser Ala Ser 2225 2230 2235 2240
Trp Val Asp Val Asp Ala Thr Gly Lys Val Thr Phe Lys Asn Val Gly 2245 2250 2255
Ser Asn Ser Glu Arg Ile Thr Ala Thr Pro Lys Ser Gly Gly Pro Ser 2260 2265 2270
Tyr Val Tyr Glu Ile Arg Val Lys Ser Trp Trp Val Asn Ala Gly Glu 2275 2280 2285
Ala Phe Met Ile Tyr Ser Leu Ala Glu Asn Phe Cys Ser Ser Asn Gly 2290 2295 2300
Tyr Thr Leu Pro Arg Ala Asn Tyr Leu Asn His Cys Ser Ser Arg Gly 2305 2310 2315 2320
Ile Gly Ser Leu Tyr Ser Glu Trp Gly Asp Met Gly His Tyr Thr Thr
2325 2330 2335
Asp Ala Gly Phe Gln Ser Asn Met Tyr Trp Ser Ser Ser Pro Ala Asn 2340 2345 2350
Ser Ser Glu Gln Tyr Val Val Ser Leu Ala Thr Gly Asp Gln Ser Val
2355 2360 2365
Phe Glu Lys Leu Gly Phe Ala Tyr Ala Thr Cys Tyr Lys Asn Leu
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                          2375
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<213> E. Coli

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<210> 304 <211> 398 <212> PRT <213> E. Coli

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35 40 45 Asn Asp Pro Ala Ala Gly Thr Thr Gly Pro Trp Tyr Thr Asn Gly Thr 55

Phe Gly Leu Thr Ala Gly Trp His Leu Asp Ile Trp Gly Lys Asn Arg 65 70 75 80 Ala Glu Val Thr Ala Arg Leu Gly Thr Val Lys Ala Arg Ala Ala Glu 85 90 95 Arg Glu Gln Thr Arg Gln Leu Leu Ala Gly Ser Val Ala Arg Leu Tyr 100 105 110 Trp Glu Trp Gln Thr Gln Ala Ala Leu Asn Thr Val Leu Gln Gln Ile 115 120 125 Glu Lys Glu Gln Asn Thr Ile Ile Ala Thr Asp Arg Gln Leu Tyr Gln 130 135 140 Asn Gly Ile Thr Ser Ser Val Glu Gly Val Glu Thr Asp Ile Asn Ala 145 150 155 160 Ser Lys Thr Arg Gln Gln Leu Asn Asp Val Ala Gly Lys Met Lys Ile 165 170 175 Ile Glu Ala Arg Leu Ser Ala Leu Thr Asn Asn Gln Thr Lys Ser Leu 180 185 190 Lys Leu Lys Pro Val Ala Leu Pro Lys Val Ala Ser Gln Leu Pro Asp 195 200 205 Glu Leu Gly Tyr Ser Leu Leu Ala Arg Arg Ala Asp Leu Gln Ala Ala 210 215 220 His Trp Tyr Val Glu Ser Ser Leu Ser Thr Ile Asp Ala Ala Lys Ala 225 230 235 240 Ala Phe Tyr Pro Asp Ile Asn Leu Met Ala Phe Leu Gln Gln Asp Ala 245 250 255 Leu His Leu Ser Asp Leu Phe Arg His Ser Ala Gln Gln Met Gly Val 260 265 270 Thr Ala Gly Leu Thr Leu Pro Ile Phe Asp Ser Gly Arg Leu Asn Ala 275 280 285 Asn Leu Asp Ile Ala Lys Ala Glu Ser Asn Leu Ser Ile Ala Ser Tyr 290 295 300 Asn Lys Ala Val Val Glu Ala Val Asn Asp Val Ala Arg Ala Ala Ser 305 310 315 320 Gln Val Gln Thr Leu Ala Glu Lys Asn Gln His Gln Ala Gln Ile Glu 325 330 335 Arg Asp Ala Leu Arg Val Val Gly Leu Ala Gln Ala Arg Phe Asn Ala 340 345 350 Gly Ile Ile Ala Gly Ser Arg Val Ser Glu Ala Arg Ile Pro Ala Leu 355 360 365 Arg Glu Arg Ala Asn Gly Leu Leu Gln Gly Gln Trp Leu Asp Ala 370 375 380 Ser Ile Gln Leu Thr Gly Ala Leu Gly Gly Gly Tyr Lys Arg 385 390 395

<210> 305 <211> 96 <212> PRT

<213> E. Coli

85 90 95

<210> 306 <211> 315 <212> PRT <213> E. Coli

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<210> 307 <211> 296 <212> PRT <213> E. Coli

<400> 307

Met Thr Ile Ser Thr Thr Ser Thr Pro His Asp Ala Val Phe Lys Ser 1 5 10 15 Phe Leu Arg His Pro Asp Thr Ala Arg Asp Phe Ile Asp Ile His Leu 20 25 30

Pro Ala Pro Leu Arg Lys Leu Cys Asp Leu Thr Thr Leu Lys Leu Glu 35 40 45 Pro Asn Ser Phe Ile Asp Glu Asp Leu Arg Gln Tyr Tyr Ser Asp Leu 50 55 Leu Trp Ser Val Lys Thr Gin Glu Gly Val Gly Tyr Ile Tyr Val Val 65 70 80 Ile Glu His Gln Ser Lys Pro Glu Glu Leu Met Ala Phe Arg Met Met 85 90 95 Arg Tyr Ser Ile Ala Ala Met Gln Asn His Leu Asp Ala Gly Tyr Lys
100 105 110

Glu Leu Pro Leu Val Leu Pro Met Leu Phe Tyr His Gly Cys Arg Ser
115 120 125 Pro Tyr Pro Tyr Ser Leu Cys Trp Leu Asp Glu Phe Ala Glu Pro Ala 130 135 140 Ile Ala Arg Lys Ile Tyr Ser Ser Ala Phe Pro Leu Val Asp Ile Thr 145 150 155 160 Val Val Pro Asp Asp Glu Ile Met Gln His Arg Lys Met Ala Leu Leu 165 170 175 Glu Leu Ile Gln Lys His Ile Arg Gln Arg Asp Leu Leu Gly Leu Val 180 185 190 Asp Gln Ile Val Ser Leu Leu Val Thr Gly Asn Thr Asn Asp Arg Gln
195 200 205 .

Leu Lys Ala Leu Phe Asn Tyr Val Leu Gln Thr Gly Asp Ala Gln Arg
210 215 220 Phe Arg Ala Phe Ile Gly Glu Ile Ala Glu Arg Ala Pro Gln Glu Lys 225 230 235 240 Glu Lys Leu Met Thr Ile Ala Asp Arg Leu Arg Glu Glu Gly Ala Met 245 250 255 Gln Gly Lys His Glu Glu Ala Leu Arg Ile Ala Gln Glu Met Leu Asp 260 265 270 Arg Gly Leu Asp Arg Glu Leu Val Met Met Val Thr Arg Leu Ser Pro 275 280 285 285 Asp Asp Leu Ile Ala Gln Ser His 290 295

<210> 308 <211> 555 <212> PRT <213> E. Coli

<400> 308

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Glu Arg Ala Ala Asp Ala Leu Arg Leu Pro Asp Trp Asp Ala Lys Ile
145 150 155 160
Ala Asn Leu Ser Gly Gly Glu Arg Arg Val Ala Leu Cys Arg Leu
165 170 175
Leu Leu Glu Lys Pro Asp Met Leu Leu Leu Asp Glu Pro Thr Asn His
180 185 190
Leu Asp Ala Glu Ser Val Ala Trp Leu Glu Arg Phe Leu His Asp Phe
195 200 205
Glu Gly Thr Val Val Ala Ile Thr His Asp Arg Tyr Phe Leu Asp Asn 210 220

Val Ala Gly Trp Ile Leu Glu Leu Asp Arg Gly Glu Gly Ile Pro Trp 225 230 235 240
Glu Gly Asn Tyr Ser Ser Trp Leu Glu Gln Lys Asp Gln Arg Leu Ala
245 250 255
Gln Glu Ala Ser Gln Glu Ala Ala Arg Arg Lys Ser Ile Glu Lys Glu
260 265 270
Leu Glu Trp Val Arg Gln Gly Thr Lys Gly Arg Gln Ser Lys Gly Lys
275 280 285
Ala Arg Leu Ala Arg Phe Glu Glu Leu Asn Ser Thr Glu Tyr Gln Lys
290 . 295 300
Arg Asn Glu Thr Asn Glu Leu Phe Ile Pro Pro Gly Pro Arg Leu Gly 305 310 315 320
Asp Lys Val Leu Glu Val Ser Asn Leu Arg Lys Ser Tyr Gly Asp Arg
325 330 335
Leu Leu Ile Asp Asp Leu Ser Phe Ser Ile Pro Lys Gly Ala Ile Val
340 345 350
Gly Ile Ile Gly Pro Asn Gly Ala Gly Lys Ser Thr Leu Phe Arg Met 355 360 365
Ile Ser Gly Gln Gln Gln Pro Asp Ser Gly Thr Ile Thr Leu Gly Glu 370 375 380
Thr Val Lys Leu Ala Ser Val Asp Gln Phe Arg Asp Ser Met Asp Asn 385 390 395 400
Ser Lys Thr Val Trp Glu Glu Val Ser Gly Gly Leu Asp Ile Met Lys
405 410 415
Ile Gly Asn Thr Glu Met Pro Ser Arg Ala Tyr Val Gly Arg Phe Asn 420 425 430
Phe Lys Gly Val Asp Gln Gly Lys Arg Val Gly Glu Leu Ser Gly Gly 435 440 445
Glu Arg Gly Arg Leu His Leu Ala Lys Leu Leu Gln Val Gly Gly Asn
450 455 460
Met Leu Leu Leu Asp Glu Pro Thr Asn Asp Leu Asp Ile Glu Thr Leu
465 470 475 480
Arg Ala Leu Glu Asn Ala Leu Leu Glu Phe Pro Gly Cys Ala Met Val
485 490 495
The Ser His Asp Arg Trp Phe Leu Asp Arg The Ala Thr His The Leu 500 505 510
Asp Tyr Gln Asp Glu Gly Lys Val Glu Phe Phe Glu Gly Asn Phe Thr 515 520 525
Glu Tyr Glu Glu Tyr Lys Lys Arg Thr Leu Gly Ala Asp Ala Leu Glu
530 535 540
Pro Lys Arg Ile Lys Tyr Lys Arg Ile Ala Lys
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<400> 309

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 Ser
 Lys
 Pro
 Lys
 Pro
 Phe
 Glu
 Lys
 Arg
 Leu
 Glu
 Val
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<210> 310 <211> 283 <212> PRT <213> E. Coli

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245
                                         250
Tyr Asn Ser Arg Arg Ile Ser Leu Lys Leu Lys Gly Leu Thr Pro Ile
            260
                           265
Glu Tyr Arg Asn Gln Thr Tyr Met Pro Arg Val
       <210> 311
       <211> 38
<212> PRT
       <213> E. Coli
       <400> 311
Met Lys Val Arg Ala Ser Val Lys Lys Leu Cys Arg Asn Cys Lys Ile
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Val Lys Arg Asp Gly Val Ile Arg Val Ile Cys Ser Ala Glu Pro Lys
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                                    25
His Lys Gln Arg Gln Gly
        35
       <210> 312
       <211> 443
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       <213> E. Coli
       <400> 312
Met Ala Lys Gln Pro Gly Leu Asp Phe Gln Ser Ala Lys Gly Gly Leu
1 5 10 15
Gly Glu Leu Lys Arg Arg Leu Leu Phe Val Ile Gly Ala Leu Ile Val
20 25 30
Phe Arg Ile Gly Ser Phe Ile Pro Ile Pro Gly Ile Asp Ala Ala Val
35 40 45
Leu Ala Lys Leu Leu Glu Gln Gln Arg Gly Thr Ile Ile Glu Met Phe 50 55 60
Asn Met Phe Ser Gly Gly Ala Leu Ser Arg Ala Ser Ile Phe Ala Leu 65 70 75 80
Gly Ile Met Pro Tyr Ile Ser Ala Ser Ile Ile Ile Gln Leu Leu Thr 85 . 90 95
Val Val His Pro Thr Leu Ala Glu Ile Lys Lys Glu Gly Glu Ser Gly 100 105 110
Arg Arg Lys Ile Ser Gln Tyr Thr Arg Tyr Gly Thr Leu Val Leu Ala
115 120 125
Ile Phe Gln Ser Ile Gly Ile Ala Thr Gly Leu Pro Asn Met Pro Gly 130 135 140
Met Gin Gly Leu Val Ile Asn Pro Gly Phe Ala Phe Tyr Phe Thr Ala
145 150 155 160
Val Val Ser Leu Val Thr Gly Thr Met Phe Leu Met Trp Leu Gly Glu
165 170 175
Gln Ile Thr Glu Arg Gly Ile Gly Asn Gly Ile Ser Ile Ile Ile Phe
180 185 190
Ala Giy Ile Val Ala Gly Leu Pro Pro Ala Ile Ala His Thr Ile Glu 195 200 205
Gln Ala Arg Gln Gly Asp Leu His Phe Leu Val Leu Leu Val Ala 210 \phantom{\bigg|}215\phantom{\bigg|} 220
Val Leu Val Phe Ala Val Thr Phe Phe Val Val Phe Val Glu Arg Gly 225 230 235 240
Gln Arg Arg Ile Val Val Asn Tyr Ala Lys Arg Gln Gln Gly Arg Arg
245 250 255
Val Tyr Ala Ala Gln Ser Thr His Leu Pro Leu Lys Val Asn Met Ala 260 265 270
Gly Val Ile Pro Ala Ile Phe Ala Ser Ser Ile Ile Leu Phe Pro Ala
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<210> 313 <211> 144 <212> PRT <213> E. Coli

<400> 313

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 Thr
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 Gly
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 Lys
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 Ala
 Gly
 Inchmoss
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<210> 314 <211> 59 <212> PRT <213> E. Coli

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<210> 315 <211> 167 <212> PRT <213> E. Coli

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<210> 316 <211> 117 <212> PRT <213> E. Coli

<210> 317 <211> 177

<212> PRT <213> E. Coli

<210> 318 <211> 130 <212> PRT <213> E. Coli

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 Asp Met Leu Thr Arg Ile Arg Asn 15

 Gly Gln Ala Ala Asn Lys Ala Ala Val Thr Met Pro Ser Ser Lys Leu 20
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 Lys Val Ala Ile Ala Asn Val Leu Lys Glu Glu Gly Phe Ile Glu Asp 35
 40

 Phe Lys Val Glu Gly Asp Thr Lys Pro Glu Leu Glu Leu Thr Leu Lys 50
 55

 Tyr Phe Gln Gly Lys Ala Val Val Glu Ser Ile Gln Arg Val Ser Arg 65
 70

 Pro Gly Leu Arg Ile Tyr Lys Arg Lys Asp Glu Leu Pro Lys Val Met 85
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 Ala Gly Leu Gly Ile Ala Val Val Ser Thr Ser Lys Gly Val Met 110

 Asp Arg Ala Ala Arg Gln Ala Gly Leu Gly Gly Glu Ile Ile Cys Tyr 115

 Val Ala

<210> 319 <211> 101 <212> PRT <213> E. Coli

<210> 320 <211> 179 <212> PRT <213> E. Coli

<210>_321Z <211> 104 <212> PRT <213> E. Coli

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 Met Ala Ala Lys Ile Arg Arg Asp Asp Glu Val Ile Val Leu Thr Gly

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 Lys Asp Lys Gly Lys Arg Gly Lys Val Lys Asn Val Leu Ser Ser Gly

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<210> 322 <211> 123 <212> PRT <213> E. Coli

 400> 322

 Met Ile Gln Glu Glu Gln Thr Met Leu Asn Val Ala Asp Asn Ser Gly Ala 1

 Arg Arg Val Met Cys Ile Lys Val Leu Gly Gly Ser His Arg Tyr 20

 Ala Gly Val Gly Asp Ile Ile Lys Ile Thr Ile Lys Glu Ala Ile Pro 35

 Arg Gly Lys Val Lys Lys Gly Asp Val Leu Lys Ile Thr Ile Lys Glu Ala Ile Pro 55

 Arg Gly Lys Gly Val Lys Lys Gly Asp Val Leu Lys Ala Val Val Arg 50

 Thr Lys Lys Gly Val Arg Arg Pro Asp Gly Ser Val Ile Arg Phe Asp 65

 Gly Asn Ala Cys Val Leu Leu Asn Asn Asn Ser Glu Gln Pro Ile Gly 85

 Thr Arg Ile Phe Gly Pro Val Thr Arg Glu Leu Arg Ser Glu Lys Phe 100

 Met Lys Ile Ile Ser Leu Ala Pro Glu Val Leu

<210> 323 <211> 188 <212> PRT <213> E. Coli

<400> 323

 Met
 Phe
 Lys
 Gly
 Gln
 Lys
 Thr
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 Ala</th

> <210> 324 <211> 427 <212> PRT <213> E. Coli

<400> 324 Met Ala Asp Thr Lys Ala Lys Leu Thr Leu Asn Gly Asp Thr Ala Val $1 \hspace{1cm} 5 \hspace{1cm} 10 \hspace{1cm} 15$ Glu Leu Asp Val Leu Lys Gly Thr Leu Gly Gln Asp Val Ile Asp Ile 20 25 30 Arg Thr Leu Gly Ser Lys Gly Val Phe Thr Phe Asp Pro Gly Phe Thr 35 40 45 Ser Thr Ala Ser Cys Glu Ser Lys Ile Thr Phe Ile Asp Gly Asp Glu 50 60 Gly Ile Leu Leu His Arg Gly Phe Pro Ile Asp Gln Leu Ala Thr Asp 65 70 75 80 Ser Asn Tyr Leu Glu Val Cys Tyr Ile Leu Leu Asn Gly Glu Lys Pro 85 90 95 Thr Gln Glu Gln Tyr Asp Glu Phe Lys Thr Thr Val Thr Arg His Thr Met Ile His Glu Gln Ile Thr Arg Leu Phe His Ala Phe Arg Arg Asp 115 120 125 Ser His Pro Met Ala Val Met Cys Gly Ile Thr Gly Ala Leu Ala Ala 130 135 140 Phe Tyr His Asp Ser Leu Asp Val Asn Asn Pro Arg His Arg Glu Ile 145 150 155 160 Ala Ala Phe Arg Leu Leu Ser Lys Met Pro Thr Met Ala Ala Met Cys 165 170 175 Tyr Lys Tyr Ser Ile Gly Gln Pro Phe Val Tyr Pro Arg Asn Asp Leu 180 185 190 Ser Tyr Ala Gly Asn Phe Leu Asn Met Met Phe Ser Thr Pro Cys Glu 195 200 205 Pro Tyr Glu Val Asn Pro Ile Leu Glu Arg Ala Met Asp Arg Ile Leu 210 215 220 Ile Leu His Ala Asp His Glu Gln Asn Ala Ser Thr Ser Thr Val Arg 225 230 . 235 240 225 Thr Ala Gly Ser Ser Gly Ala Asn Pro Phe Ala Cys Ile Ala Ala Gly 245 250 255 Ile Ala Ser Leu Trp Gly Pro Ala His Gly Gly Ala Asn Glu Ala Ala 260 265 270 Leu Lys Met Leu Glu Glu Ile Ser Ser Val Lys His Ile Pro Glu Phe 275 280 285 Val Arg Arg Ala Lys Asp Lys Asn Asp Ser Phe Arg Leu Met Gly Phe 290 295 300 Gly His Arg Val Tyr Lys Asn Tyr Asp Pro Arg Ala Thr Val Met Arg 305 310 315 320 Glu Thr Cys His Glu Val Leu Lys Glu Leu Gly Thr Lys Asp Asp Leu 325 330 335 Leu Glu Val Ala Met Glu Leu Glu Asn Ile Ala Leu Asn Asp Pro Tyr 340 350 Phe Ile Glu Lys Lys Leu Tyr Pro Asn Val Asp Phe Tyr Ser Gly Ile 355 360 365 Ile Leu Lys Ala Met Gly Ile Pro Ser Ser Met Phe Thr Val Ile Phe 375

Ala Met Ala Arg Thr Val Gly Trp Ile Ala His Trp Ser Glu Met His 385 390 395 400

Ser Asp Gly Met Lys Ile Ala Arg Pro Arg Gln Leu Tyr Thr Gly Tyr 405 410 415

Glu Lys Arg Asp Phe Lys Ser Asp Ile Lys Arg 420 425

<210> 325 <211> 477 <212> PRT <213> E. Coli

<400> 325 Met Lys Val Thr Leu Pro Glu Phe Glu Arg Ala Gly Val Met Val Val 1 5 10 15 Gly Asp Val Met Leu Asp Arg Tyr Trp Tyr Gly Pro Thr Ser Arg Ile 20 25 30 Ser Pro Glu Ala Pro Val Pro Val Val Lys Val Asn Thr Ile Glu Glu 35 40 45 Arg Pro Gly Gly Ala Ala Asn Val Ala Met Asn Ile Ala Ser Leu Gly 50 55 60 Ala Asn Ala Arg Leu Val Gly Leu Thr Gly Ile Asp Asp Ala Ala Arg 65 70 75 80 Ala Leu Ser Lys Ser Leu Ala Asp Val Asn Val Lys Cys Asp Phe Val 85 90 95 Ser Val Pro Thr His Pro Thr Ile Thr Lys Leu Arg Val Leu Ser Arg Asn Gln Gln Leu Ile Arg Leu Asp Phe Glu Glu Gly Phe Glu Gly Val 115 120 125 Asp Pro Gln Pro Leu His Glu Arg Ile Asn Gln Ala Leu Ser Ser Ile 130 135 140 Gly Ala Leu Val Leu Ser Asp Tyr Ala Lys Gly Ala Leu Ala Ser Val 145 150 155 160 Gln Gln Met Ile Gln Leu Ala Arg Lys Ala Gly Val Pro Val Leu Ile 165 170 175 Asp Pro Lys Gly Thr Asp Phe Glu Arg Tyr Arg Gly Ala Thr Leu Leu 180 . 185 190 Thr Pro Asn Leu Ser Glu Phe Glu Ala Val Val Gly Lys Cys Lys Thr 195 200 205 Glu Glu Glu Ile Val Glu Arg Gly Met Lys Leu Ile Ala Asp Tyr Glu 210 215 220 Leu Ser Ala Leu Leu Val Thr Arg Ser Glu Gln Gly Met Ser Leu Leu 225 230 235 240 Gln Pro Gly Lys Ala Pro Leu His Met Pro Thr Gln Ala Gln Glu Val 245 250 255 Tyr Asp Val Thr Gly Ala Gly Asp Thr Val Ile Gly Val Leu Ala Ala 260 265 270 Thr Leu Ala Ala Gly Asn Ser Leu Glu Glu Ala Cys Phe Phe Ala Asn 275 280 285 Ala Ala Ala Gly Val Val Val Gly Lys Leu Gly Thr Ser Thr Val Ser 290 295 300 Pro Ile Glu Leu Glu Asn Ala Val Arg Gly Arg Ala Asp Thr Gly Phe 305 310 315 320 Gly Val Met Thr Glu Glu Glu Leu Lys Leu Ala Val Ala Ala Ala Arg 325 330 335 325 330 Lys Arg Gly Glu Lys Val Val Met Thr Asn Gly Val Phe Asp Ile Leu 340 345 350 His Ala Gly His Val Ser Tyr Leu Ala Asn Ala Arg Lys Leu Gly Asp 355 360 365 Arg Leu Ile Val Ala Val Asn Ser Asp Ala Ser Thr Lys Arg Leu Lys

<210> 326 <211> 946 <212> PRT <213> E. Coli

<400> 326 Met Lys Pro Leu Ser Ser Pro Leu Gln Gln Tyr Trp Gln Thr Val Val 1 5 10 15 Glu Arg Leu Pro Glu Pro Leu Ala Glu Glu Ser Leu Ser Ala Gln Ala 20 25 30 Lys Ser Val Leu Thr Phe Ser Asp Phe Val Gln Asp Ser Val Ile Ala 35 40 45 His Pro Glu Trp Leu Thr Glu Leu Glu Ser Gln Pro Pro Gln Ala Asp
50 55 60 Glu Trp Gln His Tyr Ala Ala Trp Leu Gln Glu Ala Leu Cys Asn Val 65 70 75 80 Ser Asp Glu Ala Gly Leu Met Arg Glu Leu Arg Leu Phe Arg Arg Arg 90 95 Ile Met Val Arg Ile Ala Trp Ala Gln Thr Leu Ala Leu Val Thr Glu 100 105 110 Glu Ser Ile Leu Gln Gln Leu Ser Tyr Leu Ala Glu Thr Leu Ile Val 115 120 125 Ala Ala Arg Asp Trp Leu Tyr Asp Ala Cys Cys Arg Glu Trp Gly Thr 130 135 140 Pro Cys Asn Ala Gln Gly Glu Ala Gln Pro Leu Leu Ile Leu Gly Met 145 150 155 160 Gly Lys Leu Gly Gly Gly Glu Leu Asn Phe Ser Ser Asp Ile Asp Leu 165 170 175

Ile Phe Ala Trp Pro Glu His Gly Cys Thr Gln Gly Gly Arg Arg Glu 180 190 Leu Asp Asn Ala Gln Phe Phe Thr Arg Met Gly Gln Arg Leu Ile Lys 195 200 205 Val Leu Asp Gln Pro Thr Gln Asp Gly Phe Val Tyr Arg Val Asp Met 210 215 220 Arg Leu Arg Pro Phe Gly Glu Ser Gly Pro Leu Val Leu Ser Phe Ala 225 230 235 240 Ala Leu Glu Asp Tyr Tyr Gln Glu Gln Gly Arg Asp Trp Glu Arg Tyr
245 250 255 Ala Met Val Lys Ala Arg Ile Met Gly Asp Ser Glu Gly Val Tyr Ala 260 265 270 Asn Glu Leu Arg Ala Met Leu Arg Pro Phe Val Phe Arg Arg Tyr Ile 275 280 285 Asp Phe Ser Val Ile Gln Ser Leu Arg Asn Met Lys Gly Met Ile Ala 290 295 300 Arg Glu Val Arg Arg Arg Gly Leu Thr Asp Asn Ile Lys Leu Gly Ala 315

Gly Gly Ile Arg Glu Ile Glu Phe Ile Val Gln Val Phe Gln Leu Ile 325 330 335 Arg Gly Gly Arg Glu Pro Ser Leu Gln Ser Arg Ser Leu Leu Pro Thr Leu Ser Ala Ile Ala Glu Leu His Leu Leu Ser Glu Asn Asp Ala Glu 355 360 365 Gln Leu Arg Val Ala Tyr Leu Phe Leu Arg Arg Leu Glu Asn Leu Leu 370 380 Gln Ser Ile Asn Asp Glu Gln Thr Gln Thr Leu Pro Ser Asp Glu Leu 385 390 395 400
Asn Arg Ala Arg Leu Ala Trp Ala Met Asp Phe Ala Asp Trp Pro Gln 405 410 415 Leu Thr Gly Ala Leu Thr Ala His Met Thr Asn Val Arg Arg Val Phe 420 425 430 Asn Glu Leu Ile Gly Asp Asp Glu Ser Glu Thr Gln Glu Glu Ser Leu 435 440 445 Ser Glu Gln Trp Arg Glu Leu Trp Gln Asp Ala Leu Gln Glu Asp Asp 450 455 460 Thr Thr Pro Val Leu Ala His Leu Ser Glu Asp Asp Arg Lys Gln Val 465 470 475 480 Leu Thr Leu Ile Ala Asp Phe Arg Lys Glu Leu Asp Lys Arg Thr Ile 485 490 495 Gly Pro Arg Gly Arg Gln Val Leu Asp His Leu Met Pro His Leu Leu 500 505 510 Ser Asp Val Cys Ala Arg Glu Asp Ala Ala Val Thr Leu Ser Arg Ile 515 520 525 Thr Ala Leu Leu Val Gly Ile Val Thr Arg Thr Thr Tyr Leu Glu Leu 530 535 540 Leu Ser Glu Phe Pro Ala Ala Leu Lys His Leu Ile Ser Leu Cys Ala 545 550 555 560 Ala Ser Pro Met Ile Ala Ser Gln Leu Ala Arg Tyr Pro Leu Leu Leu 565 570 575 Asp Glu Leu Leu Asp Pro Asn Thr Leu Tyr Gln Pro Thr Ala Thr Asp 580 585 590 Ala Tyr Arg Asp Glu Leu Arg Gln Tyr Leu Leu Arg Val Pro Glu Asp 595 600 605 Asp Glu Glu Gln Gln Leu Glu Ala Leu Arg Gln Phe Lys Gln Ala Gln 610 615 620 Leu Leu Arg Ile Ala Ala Ala Asp Ile Ala Gly Thr Leu Pro Val Met 625 630 635 640 Lys Val Ser Asp His Leu Thr Trp Leu Ala Glu Ala Met Ile Asp Ala 645 650 655 Val Val Gln Gln Ala Trp Val Gln Met Val Ala Arg Tyr Gly Lys Pro 660 665 670 Asn His Leu Asn Glu Arg Glu Gly Arg Gly Phe Ala Val Val Gly Tyr 675 680 685 Gly Lys Leu Gly Gly Trp Glu Leu Gly Tyr Ser Ser Asp Leu Asp Leu 690 695 700 Ile Phe Leu His Asp Cys Pro Met Asp Ala Met Thr Asp Gly Glu Arg 705 710 715 720 Glu Ile Asp Gly Arg Gln Phe Tyr Leu Arg Leu Ala Gln Arg Ile Met
725 730 735 His Leu Phe Ser Thr Arg Thr Ser Ser Gly Ile Leu Tyr Glu Val Asp
740 745 750 Ala Arg Leu Arg Pro Ser Gly Ala Ala Gly Met Leu Val Thr Ser Ala
755 760 765 Glu Ala Phe Ala Asp Tyr Gln Lys Asn Glu Ala Trp Thr Trp Glu His 770 780 Gln Ala Leu Val Arg Ala Arg Val Val Tyr Gly Asp Pro Gln Leu Thr 785 790 795 800 Ala His Phe Asp Ala Val Arg Arg Glu Ile Met Thr Leu Pro Arg Glu

Gly Lys Thr Leu Gln Thr Glu Val Arg Glu Met Arg Glu Lys Met Arg 825

Ala His Leu Gly Asn Lys His Arg Asp Arg Phe Asp Ile Lys Ala Asp 845

Glu Gly Gly Ile Thr Asp Ile Glu Phe Ile Thr Gln Tyr Leu Val Leu 850

Arg Tyr Ala His Glu Lys Pro Lys Leu Thr Arg Tyr Ser Asp Asn Val 865

Arg Ile Leu Glu Leu Leu Ala Gln Asn Asp Ile Met Glu Glu Glu Glu 895

Ala Met Ala Leu Thr Arg Ala Tyr Thr Thr Leu Arg Asp Glu Leu His 900

His Leu Ala Glu Arg Glu Leu Val Arg Ala Ser Tyr Gln Lys Tyr Leu Val 930

Glu Glu 935

<210> 327 <211> 433 <212> PRT <213> E. Coli

<400> 327 Met Ala Gln Glu Ile Glu Leu Lys Phe Ile Val Asn His Ser Ala Val 5 10 Glu Ala Leu Arg Asp His Leu Asn Thr Leu Gly Gly Glu His His Asp 20 25 30 Pro Val Gln Leu Leu Asn Ile Tyr Tyr Glu Thr Pro Asp Asn Trp Leu 35 40 45 Arg Gly His Asp Met Gly Leu Arg Ile Arg Gly Glu Asn Gly Arg Tyr 50 60 Glu Met Thr Met Lys Val Ala Gly Arg Val Thr Gly Gly Leu His Gln 65 70 80 Arg Pro Glu Tyr Asn Val Ala Leu Ser Glu Pro Thr Leu Asp Leu Ala 85 90 95 Gln Leu Pro Thr Glu Val Trp Pro Asn Gly Glu Leu Pro Ala Asp Leu 100 105 110 Ala Ser Arg Val Gln Pro Leu Phe Ser Thr Asp Phe Tyr Arg Glu Lys 115 120 125 Trp Leu Val Ala Val Asp Gly Ser Gln Ile Glu Ile Ala Leu Asp Gln 130 135 140 Gly Glu Val Lys Ala Gly Glu Phe Ala Glu Pro Ile Cys Glu Leu Glu 145 150 155 160 Leu Glu Leu Leu Ser Gly Asp Thr Arg Ala Val Leu Lys Leu Ala Asn 165 170 175 Gln Leu Val Ser Gln Thr Gly Leu Arg Gln Gly Ser Leu Ser Lys Ala 180 185 190 Ala Arg Gly Tyr His Leu Ala Gln Gly Asn Pro Ala Arg Glu Ile Lys 195 200 205 Pro Thr Thr Ile Leu His Val Ala Ala Lys Ala Asp Val Glu Gln Gly 210 215 220 Leu Glu Ala Ala Leu Glu Leu Ala Leu Ala Gln Trp Gln Tyr His Glu 225 230 235 Glu Leu Trp Val Arg Gly Asn Asp Ala Ala Lys Glu Gln Val Leu Ala

245 250 255 Ala Ile Ser Leu Val Arg His Thr Leu Met Leu Phe Gly Gly Ile Val

 Pro
 Arg
 Lys
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 Tyr
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 Glu
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<210> 328 <211> 70 <212> PRT <213> E. Coli

<210> 329 <211> 523 <212> PRT <213> E. Coli

Lys Leu Phe Ser Met Leu Asn His Glu Lys Gly Leu Tyr Tyr Leu Thr 85 90 95 Arg Asp Leu Gln Cys Ser Ile Asp Pro His Asn Tyr Leu Phe Ile Leu 100 105 110 Val Cys Ala Asn Asn Ala Trp Gln Asn Ile Pro Ala Glu Arg Leu Arg 115 120 125 Ser Trp Leu Asp Lys Met Asn Lys Trp Ser Arg Leu Asn His Cys Ser 130 135 140 Leu Leu Val Ile Asn Pro Gly Asn Asn Asn Asp Lys Gln Phe Ser Leu 145 150 155 160 Leu Leu Glu Glu Tyr Arg Ser Leu Phe Gly Leu Ala Ser Leu Arg Phe 165 170 175 Gln Gly Asp Gln His Leu Leu Asp Iie Ala Phe Trp Cys Asn Glu Lys 180 185 190 Gly Val Ser Ala Arg Gln Gln Leu Ser Val Gln Gln Gln Asn Gly Ile 195 200 205 Trp Thr Leu Val Gln Ser Glu Glu Ala Glu Ile Gln Pro Arg Ser Asp 210 215 220 Glu Lys Arg Ile Leu Ser Asn Val Ala Val Leu Glu Gly Ala Pro Pro 225 230 235 240 Leu Ser Glu His Trp Gln Leu Phe Asn Asn Glu Val Leu Phe Asn 245 250 255 Glu Ala Arg Thr Ala Gln Ala Ala Thr Val Val Phe Ser Leu Gln Gln 260 265 270 270 Asn Ala Gln Ile Glu Pro Leu Ala Arg Ser Ile His Thr Leu Arg Arg 275 280 285 Gln Arg Gly Ser Ala Met Lys Ile Leu Val Arg Glu Asn Thr Ala Ser 290 295 300 Leu Arg Ala Thr Asp Glu Arg Leu Leu Leu Ala Cys Gly Ala Asn Met 305 310 315 320 Val Ile Pro Trp Asn Ala Pro Leu Ser Arg Cys Leu Thr Met Ile Glu 325 330 335 Ser Val Gln Gly Gln Lys Phe Ser Arg Tyr Val Pro Glu Asp Ile Thr 340 345 350 Thr Leu Leu Ser Met Thr Gln Pro Leu Lys Leu Arg Gly Phe Gln Lys 355 360 365 355 Trp Asp Val Phe Cys Asn Ala Val Asn Asn Met Met Asn Asn Pro Leu 370 . 375 . 380 Leu Pro Ala His Gly Lys Gly Val Leu Val Ala Leu Arg Pro Val Pro 385 390 395 400 Gly Ile Arg Val Glu Gln Ala Leu Thr Leu Cys Arg Pro Asn Arg Thr 405 410 415 Gly Asp Ile Met Thr Ile Gly Gly Asn Arg Leu Val Leu Phe Leu Ser 420 425 430 Phe Cys Arg Ile Asn Asp Leu Asp Thr Ala Leu Asn His Ile Phe Pro
435 440 445 Leu Pro Thr Gly Asp Ile Phe Ser Asn Arg Met Val Trp Phe Glu Asp 450 455 460

Asp Gln Ile Ser Ala Glu Leu Val Gln Met Arg Leu Leu Ala Pro Glu 465 470 480 Gln Trp Gly Met Pro Leu Pro Leu Thr Gln Ser Ser Lys Pro Val Ile 485 490 495 Asn Ala Glu His Asp Gly Arg His Trp Arg Arg Ile Pro Glu Pro Met 500 505 510 Arg Leu Leu Asp Asp Ala Val Glu Arg Ser Ser 520

<210> 330 <211> 62 <212> PRT

<213> E. Coli

<400> 330 Met Thr Ile Ser Asp Ile Ile Glu Ile Ile Val Val Cys Ala Leu Ile 1 5 10 15 Phe Phe Pro Leu Gly Tyr Leu Ala Arg His Ser Leu Arg Arg Ile Arg 20 25 30 Asp Thr Leu Arg Leu Phe Phe Ala Lys Pro Arg Tyr Val Lys Pro Ala 40 Gly Thr Leu Arg Arg Thr Glu Lys Ala Arg Ala Thr Lys Lys 55

<210> 331 <211> 559 <212> PRT <213> E. Coli

<400> 331 Met Thr Gln Phe Thr Gln Asn Thr Ala Met Pro Ser Ser Leu Trp Gln 1 5 10 15 Tyr Trp Arg Gly Leu Ser Gly Trp Asn Phe Tyr Phe Leu Val Lys Phe 20 25 30 Gly Leu Leu Trp Ala Gly Tyr Leu Asn Phe His Pro Leu Leu Asn Leu 35 40 45 Val Phe Ala Ala Phe Leu Leu Met Pro Leu Pro Arg Tyr Ser Leu His 50 55 60 Arg Leu Arg His Trp Ile Ala Leu Pro Ile Gly Phe Ala Leu Phe Trp 65 70 75 80 His Asp Thr Trp Leu Pro Gly Pro Glu Ser Ile Met Ser Gln Gly Ser 85 90 95 Gln Val Ala Gly Phe Ser Thr Asp Tyr Leu Ile Asp Leu Val Thr Arg 100 105 110 Phe Ile Asn Trp Gln Met Ile Gly Ala Ile Phe Val Leu Leu Val Ala 115 120 125 Trp Leu Phe Leu Ser Gln Trp Ile Arg Ile Thr Val Phe Val Val Ala 130 135 140 Ile Leu Leu Trp Leu Asn Val Leu Thr Leu Ala Gly Pro Ser Phe Ser 145 150 150 160 Leu Trp Pro Ala Gly Gln Pro Thr Thr Thr Val Thr Thr Thr Gly Gly
165 170 175 Asn Ala Ala Thr Val Ala Ala Thr Gly Gly Ala Pro Val Val Gly
180 185 190 Asp Met Pro Ala Gln Thr Ala Pro Pro Thr Thr Ala Asn Leu Asn Ala 195 200 205 Trp Leu Asn Asn Phe Tyr Asn Ala Glu Ala Lys Arg Lys Ser Thr Phe 210 215 220 215 Pro Ser Ser Leu Pro Ala Asp Ala Gln Pro Phe Glu Leu Leu Val Ile 225 230 235 240 Asn Ile Cys Ser Leu Ser Trp Ser Asp Ile Glu Ala Ala Gly Leu Met 245 250 255 Ser His Pro Leu Trp Ser His Phe Asp Ile Glu Phe Lys Asn Phe Asn 260 265 270 Ser Ala Thr Ser Tyr Ser Gly Pro Ala Ala Ile Arg Leu Leu Arg Ala 275 280 285 Ser Cys Gly Gln Thr Ser His Thr Asn Leu Tyr Gln Pro Ala Asn Asn 290 295 300 Asp Cys Tyr Leu Phe Asp Asn Leu Ser Lys Leu Gly Phe Thr Gln His 305 310 315 320 Leu Met Met Gly His Asn Gly Gln Phe Gly Gly Phe Leu Lys Glu Val

Arg Glu Asn Gly Gly Met Gln Ser Glu Leu Met Asp Gln Thr Asn Leu 340 345 350 Val Ile Leu Leu Gly Phe Asp Gly Ser Pro Val Tyr Asp Asp Thr 355 360 365 Ala Val Leu Asn Arg Trp Leu Asp Val Thr Glu Lys Asp Lys Asn Ser 370 375 380 Arg Ser Ala Thr Phe Tyr Asn Thr Leu Pro Leu His Asp Gly Asn His 385 390 395 400 Tyr Pro Gly Val Ser Lys Thr Ala Asp Tyr Lys Ala Arg Ala Gln Lys 405 410 415 Phe Phe Asp Glu Leu Asp Ala Phe Phe Thr Glu Leu Glu Lys Ser Gly 420 425 430 Arg Lys Val Met Val Val Val Pro Glu His Gly Gly Ala Leu Lys 435 440 445 Gly Asp Arg Met Gln Val Ser Gly Leu Arg Asp Ile Pro Ser Pro Ser 450 455 460 Ile Thr Asp Val Pro Val Gly Val Lys Phe Phe Gly Met Lys Ala Pro 465 470 475 480 His Gln Gly Ala Pro Ile Val Ile Glu Gln Pro Ser Ser Phe Leu Ala 485 490 495 Ile Ser Asp Leu Val Val Arg Val Leu Asp Gly Lys Ile Phe Thr Glu
500 505 510 Asp Asn Val Asp Trp Lys Lys Leu Thr Ser Gly Leu Pro Gln Thr Ala 515 520 525 Pro Val Ser Glu Asn Ser Asn Ala Val Val Ile Gln Tyr Gln Asp Lys 530 535 540 Pro Tyr Val Arg Leu Asn Gly Gly Asp Trp Val Pro Tyr Pro Gln 550

<210> 332 <211> 127 <212> PRT <213> E. Coli

<210> 333 <211> 101 <212> PRT <213> E. Coli

<400> 333 Met Ser Lys Glu His Thr Thr Glu His Leu Arg Ala Glu Leu Lys Ser

<210> 334 <211> 134 <212> PRT <213> E. Coli

<400> 334 Met Ala Asp Thr His His Ala Gln Gly Pro Gly Lys Ser Val Leu Gly 1 5 10 15 Ile Gly Gln Arg Ile Val Ser Ile Met Val Glu Met Val Glu Thr Arg 20 25 Leu Arg Leu Ala Val Val Glu Leu Glu Glu Glu Lys Ala Asn Leu Phe 35 40 45 Gln Leu Leu Met Leu Gly Leu Thr Met Leu Phe Ala Ala Phe Gly 50 55 Leu Met Ser Leu Met Val Leu Ile Ile Trp Ala Val Asp Pro Gln Tyr 65 70 . 75 80 Arg Leu Asn Ala Met Ile Ala Thr Thr Val Val Leu Leu Leu Leu Ala 85 90 95 Leu Ile Gly Gly Ile Trp Thr Leu Arg Lys Ser Arg Lys Ser Thr Leu 100 105 110 Leu Arg His Thr Arg His Glu Leu Ala Asn Asp Arg Gln Leu Leu Glu 115 120 Glu Glu Ser Arg Glu Gln 130

<210> 335 <211> 99 <212> PRT <213> E. Coli

 400> 335

 Met Ser Ser Lys
 Val Glu Arg Glu Arg Lys
 Ala Gln Leu Leu Ser 15

 Gln Ile Gln Gln Gln Arg Leu Asp Leu Ser Ala Ser Arg Arg Glu Trp 25
 30

 Leu Glu Thr Thr Gly Ala Tyr Asp Arg Arg Trp Asn Met Leu Leu Ser 35
 40

 Leu Arg Ser Trp Ala Leu Val Gly Ser Ser Val Met Ala Ile Trp Thr 50
 55

 Ile Arg His Pro Asn Met Leu Val Arg Trp Ala Arg Arg Gly Phe Gly 70
 75

 Val Trp Ser Ala Trp Arg Leu Val Lys
 Thr Thr Leu Lys Gln Gln Gln Gln 95

 Leu Arg Gly

<210> 336 <211> 160 <212> PRT <213> E. Coli <400> 336 Met Ile Leu Ser Ile Asp Ser Asn Asp Ala Asn Thr Ala Pro Leu His 1 5 10 15 Lys Lys Thr Ile Ser Ser Leu Ser Gly Ala Val Glu Ser Met Lys 20 25 30Lys Leu Glu Asp Val Gly Val Leu Val Ala Arg Ile Leu Met Pro Ile 35 40 45 Leu Phe Ile Thr Ala Gly Trp Gly Lys Ile Thr Gly Tyr Ala Gly Thr 50 55 60 Gln Gln Tyr Met Glu Ala Met Gly Val Pro Gly Phe Met Leu Pro Leu 65 70 75 80 Val Ile Leu Leu Glu Phe Gly Gly Gly Leu Ala Ile Leu Phe Gly Phe 85 90 95 Leu Thr Arg Thr Thr Ala Leu Phe Thr Ala Gly Phe Thr Leu Leu Thr 100 105 110Ala Phe Leu Phe His Ser Asn Phe Ala Glu Gly Val Asn Ser Leu Met 115 120 125 Phe Met Lys Asn Leu Thr Ile Ser Gly Gly Phe Leu Leu Leu Ala Ile 130 135 140

Thr Gly Pro Gly Ala Tyr Ser Ile Asp Arg Leu Leu Asn Lys Lys Trp

155

<210> 337 <211> 296 <212> PRT <213> E. Coli

<400> 337 Met Ile Lys Lys Thr Thr Glu Ile Asp Ala Ile Leu Leu Asn Leu Asn 1 5 10 15 Lys Ala Ile Asp Ala His Tyr Gln Trp Leu Val Ser Met Phe His Ser 20 25 30 Val Val Ala Arg Asp Ala Ser Lys Pro Glu Ile Thr Asp Asn His Ser 35 40 45 Tyr Gly Leu Cys Gln Phe Gly Arg Trp Ile Asp His Leu Gly Pro Leu 50 60 Asp Asn Asp Glu Leu Pro Tyr Val Arg Leu Met Asp Ser Ala His Gln 65 70 75 80 His Met His Asn Cys Gly Arg Glu Leu Met Leu Ala Ile Val Glu Asn 85 90 95 His Trp Gln Asp Ala His Phe Asp Ala Phe Gln Glu Gly Leu Leu Ser 100 105 110 Phe Thr Ala Ala Leu Thr Asp Tyr Lys Ile Tyr Leu Leu Thr Ile Arg 115 120 125 Ser Asn Met Asp Val Leu Thr Gly Leu Pro Gly Arg Arg Val Leu Asp 130 135 140 Glu Ser Phe Asp His Gln Leu Arg Asn Ala Glu Pro Leu Asn Leu Tyr 145 150 155 160 Leu Met Leu Leu Asp Ile Asp Arg Phe Lys Leu Val Asn Asp Thr Tyr 165 170 175

<210> 338 <211> 203 <212> PRT <213> E. Coli

<400> 338 Met Arg Leu Arg Val Val Pro Gly Phe Ile Ser Pro Pro Pro Gly Phe 1 5 10 15 Gly Gly Leu Gly Tyr Thr Pro Thr Ala Arg Ala Cys Val Asn Ile Ser 20 25 30 Ile Pro Leu Gin Leu Arg Val Ile Asp Met Leu Asp Val Phe Thr Pro 35 40 45 Leu Leu Lys Leu Phe Ala Asn Glu Pro Leu Glu Arg Leu Met Tyr Thr 50 55 60 Ile Ile Ile Phe Gly Leu Thr Leu Trp Leu Ile Pro Lys Glu Phe Thr 65 70 75 80 Val Ala Phe Asn Ala Tyr Thr Glu Ile Pro Trp Leu Phe Gln Ile Ile 85 90 95 Val Phe Ala Phe Ser Phe Val Val Ala Ile Ser Phe Ser Arg Leu Arg Ala His Ile Gln Lys His Tyr Ser Leu Leu Pro Glu Gln Arg Val Leu 115 120 125 Leu Arg Leu Ser Glu Lys Glu Ile Ala Val Phe Lys Asp Phe Leu Lys 130 135 140 Thr Gly Asn Leu Ile Ile Thr Ser Pro Cys Arg Asn Pro Val Met Lys 145 150 155 160 Lys Leu Glu Arg Lys Gly Ile Ile Gln His Gln Ser Asp Ser Ala Asn 165 170 175 Cys Ser Tyr Tyr Leu Val Thr Glu Lys Tyr Ser His Phe Met Lys Leu 180 185 190 Phe Trp Asn Ser Arg Ser Arg Arg Phe Asn Arg 195 200

<210> 339 <211> 58 <212> PRT <213> E. Coli

 $<\!400\!>$ 339 Met Leu Gln Pro Ser Ala Arg Thr Ser Phe Gly Phe Lys Cys Phe

1 5 10 15
Ala Phe Gly Ile Arg His Gly Ser Glu Arg Ser Ile Leu Val Gly Glu
20 25 30
His Ala Ala His Gln Gly Phe Val Val Ala Glu Val Asp Phe Leu His
35 40 45
Phe Ala Asn Leu Thr Ser Cys Cys Tyr Val
50 55

<210> 340 <211> 1426 <212> PRT <213> E. Coli

<400> 340 Met Ser Gly Lys Pro Ala Ala Arg Gln Gly Asp Met Thr Gln Tyr Gly
1 5 10 15 Gly Pro Ile Val Gln Gly Ser Ala Gly Val Arg Ile Gly Ala Pro Thr 20 25 30 Gly Val Ala Cys Ser Val Cys Pro Gly Gly Met Thr Ser Gly Asn Pro 35 40 45 Val Asn Pro Leu Leu Gly Ala Lys Val Leu Pro Gly Glu Thr Asp Leu 50 55 60 Ala Leu Pro Gly Pro Leu Pro Phe Ile Leu Ser Arg Thr Tyr Ser Ser 65 70 75 80 Tyr Arg Thr Lys Thr Pro Ala Pro Val Gly Val Phe Gly Pro Gly Trp 85 90 95 Lys Ala Pro Ser Asp Ile Arg Leu Gln Leu Arg Asp Asp Gly Leu Ile 100 105 110 Leu Asn Asp Asn Gly Gly Arg Ser Ile His Phe Glu Pro Leu Leu Pro 115 120 125 Gly Glu Ala Val Tyr Ser Arg Ser Glu Ser Met Trp Leu Val Arg Gly 130 135 140 Gly Lys Ala Ala Gln Pro Asp Gly His Thr Leu Ala Arg Leu Trp Gly 145 150 155 160 Ala Leu Pro Pro Asp Ile Arg Leu Ser Pro His Leu Tyr Leu Ala Thr 165 170 175 Asn Ser Ala Gln Gly Pro Trp Trp Ile Leu Gly Trp Ser Glu Arg Val Pro Gly Ala Glu Asp Val Leu Pro Ala Pro Leu Pro Pro Tyr Arg Val 195 200 205 Leu Thr Gly Met Ala Asp Arg Phe Gly Arg Thr Leu Thr Tyr Arg Arg 210 215 220 Glu Ala Ala Gly Asp Leu Ala Gly Glu Ile Thr Gly Val Thr Asp Gly 225 230 235 240 Ala Gly Arg Glu Phe Arg Leu Val Leu Thr Thr Gln Ala Gln Arg Ala 245 250 255 Glu Glu Ala Arg Thr Ser Ser Leu Ser Ser Ser Asp Ser Ser Arg Pro 260 265 270 Leu Ser Ala Ser Ala Phe Pro Asp Thr Leu Pro Gly Thr Glu Tyr Gly 275 280 285 Pro Asp Arg Gly Ile Arg Leu Ser Ala Val Trp Leu Met His Asp Pro 290 295 300 Ala Tyr Pro Glu Ser Leu Pro Ala Ala Pro Leu Val Arg Tyr Thr Tyr 305 310 315 320 Thr Glu Ala Gly Glu Leu Leu Ala Val Tyr Asp Arg Ser Asn Thr Gln 325 330 335 Val Arg Ala Phe Thr Tyr Asp Ala Gln His Pro Gly Arg Met Val Ala 340 345 350 His Arg Tyr Ala Gly Arg Pro Glu Met Arg Tyr Arg Tyr Asp Asp Thr 360

Gly Arg Val Val Glu Gln Leu Asn Pro Ala Gly Leu Ser Tyr Arg Tyr 370 375 380 Leu Tyr Glu Gln Asp Arg Ile Thr Val Thr Asp Ser Leu Asn Arg Arg 385 390 395 400 Glu Val Leu His Thr Glu Gly Gly Ala Gly Leu Lys Arg Val Val Lys 405 410 415 Lys Glu Leu Ala Asp Gly Ser Val Thr Arg Ser Gly Tyr Asp Ala Ala 420 425 430 Gly Arg Leu Thr Ala Gln Thr Asp Ala Ala Gly Arg Arg Thr Glu Tyr
435 440 445 Gly Leu Asn Val Val Ser Gly Asp Ile Thr Asp Ile Thr Thr Pro Asp 450 455 460 Gly Arg Glu Thr Lys Phe Tyr Tyr Asn Asp Gly Asn Gln Leu Thr Ala 465 470 475 480 Val Val Ser Pro Asp Gly Leu Glu Ser Arg Arg Glu Tyr Asp Glu Pro 485 490 495 Gly Arg Leu Val Ser Glu Thr Ser Arg Ser Gly Glu Thr Val Arg Tyr 500 505 510 Arg Tyr Asp Asp Ala His Ser Glu Leu Pro Ala Thr Thr Thr Asp Ala 515 520 525 Thr Gly Ser Thr Arg Gln Met Thr Trp Ser Arg Tyr Gly Gln Leu Leu 530 535 540 Ala Phe Thr Asp Cys Ser Gly Tyr Gln Thr Arg Tyr Glu Tyr Asp Arg 545 550 555 560 Phe Gly Gln Met Thr Ala Val His Arg Glu Glu Gly Ile Ser Leu Tyr 565 570 575 Arg Arg Tyr Asp Asn Arg Gly Arg Leu Thr Ser Val Lys Asp Ala Gln 580 585 590 Gly Arg Glu Thr Arg Tyr Glu Tyr Asn Ala Ala Gly Asp Leu Thr Ala 595 600 605 Val Ile Thr Pro Asp Gly Asn Arg Ser Glu Thr Gln Tyr Asp Ala Trp 610 615 620 Gly Lys Ala Val Ser Thr Thr Gln Gly Gly Leu Thr Arg Ser Met Glu 625 630 635 640 Tyr Asp Ala Ala Gly Arg Val Ile Ser Leu Thr Asn Glu Asn Gly Ser 645 650 655 His Ser Val Phe Ser Tyr Asp Ala Leu Asp Arg Leu Val Gln Gln Gly
660 665 670 Gly Phe Asp Gly Arg Thr Gln Arg Tyr His Tyr Asp Leu Thr Gly Lys 675 680 685 Leu Thr Gln Ser Glu Asp Glu Gly Leu Val Ile Leu Trp Tyr Tyr Asp 690 695 700 Glu Ser Asp Arg Ile Thr His Arg Thr Val Asn Gly Glu Pro Ala Glu 705 710 715 720 Gln Trp Gln Tyr Asp Gly His Gly Trp Leu Thr Asp Ile Ser His Leu 725 730 735 Ser Glu Gly His Arg Val Ala Val His Tyr Gly Tyr Asp Asp Lys Gly 740 745 750 Arg Leu Thr Gly Glu Cys Gln Thr Val Glu Asn Pro Glu Thr Gly Glu 755 760 765 Leu Leu Trp Gln His Glu Thr Lys His Ala Tyr Asn Glu Gln Gly Leu 770 775 780 Ala Asn Arg Val Thr Pro Asp Ser Leu Pro Pro Val Glu Trp Leu Thr 785 790 795 800 Tyr Gly Ser Gly Tyr Leu Ala Gly Met Lys Leu Gly Gly Thr Pro Leu 805 810 815 Val Glu Tyr Thr Arg Asp Arg Leu His Arg Glu Thr Val Arg Ser Phe 820 825 830 \cdot Gly Ser Met Ala Gly Ser Asn Ala Ala Tyr Glu Leu Thr Ser Thr Tyr 835 840 845 840 845 Thr Pro Ala Gly Gln Leu Gln Ser Gln His Leu Asn Ser Leu Val Tyr

855 860 Asp Arg Asp Tyr Gly Trp Ser Asp Asn Gly Asp Leu Val Arg Ile Ser 870 875 Gly Pro Arg Gln Thr Arg Glu Tyr Gly Tyr Ser Ala Thr Gly Arg Leu 885 890 895 Glu Ser Val Arg Thr Leu Ala Pro Asp Leu Asp Ile Arg Ile Pro Tyr 900 905 910 Ala Thr Asp Pro Ala Gly Asn Arg Leu Pro Asp Pro Glu Leu His Pro 915 920 925 Asp Ser Thr Leu Thr Val Trp Pro Asp Asn Arg Ile Ala Glu Asp Ala 930 935 940 His Tyr Val Tyr Arg His Asp Glu Tyr Gly Arg Leu Thr Glu Lys Thr 945 950 955 960 Asp Arg Ile Pro Ala Gly Val Ile Arg Thr Asp Asp Glu Arg Thr His
965
970
975
His Tyr His Tyr Asp Ser Gln His Arg Leu Val Phe Tyr Thr Arg Ile
980
985
990 Gln His Gly Glu Pro Leu Val Glu Ser Arg Tyr Leu Tyr Asp Pro Leu 995 1000 1005 Gly Arg Arg Met Ala Lys Arg Val Trp Arg Arg Glu Arg Asp Leu Thr 1010 1015 1020 Gly Trp Met Ser Leu Ser Arg Lys Pro Glu Val Thr Trp Tyr Gly Trp 1025 1030 1035 104 Asp Gly Asp Arg Leu Thr Thr Val Gln Thr Asp Thr Thr Arg Ile Gln 1045 1050 1055 1040 Thr Val Tyr Glu Pro Gly Ser Phe Thr Pro Leu Ile Arg Val Glu Thr Glu Asn Gly Glu Arg Glu Lys Ala Gln Arg Arg Ser Leu Ala Glu Thr 1075 1080 1085 Leu Gln Gln Glu Gly Ser Glu Asn Gly His Gly Val Val Phe Pro Ala 1090 1095 1100 Glu Leu Val Arg Leu Leu Asp Arg Leu Glu Glu Glu Ile Arg Ala Asp 1105 1110 1115 112 Arg Val Ser Ser Glu Ser Arg Ala Trp Leu Ala Gln Cys Gly Leu Thr 1125 1130 1135 Val Glu Gln Leu Ala Arg Gln Val Glu Pro Glu Tyr Thr Pro Ala Arg 1140 1145 1150 Lys Ala His Leu Tyr His Cys Asp His Arg Gly Leu Pro Leu Ala Leu 1155 1160 1165 Ile Ser Glu Asp Gly Asn Thr Ala Trp Ser Ala Glu Tyr Asp Glu Trp 1170 1175 1180 1180 Gly Asn Gln Leu Asn Glu Glu Asn Pro His His Val Tyr Gln Pro Tyr 1185 1190 1195 120 Arg Leu Pro Gly Gln Gln His Asp Glu Glu Ser Gly Leu Tyr Tyr Asn
1205
1210
1215
Arg His Arg Tyr Tyr Asp Pro Leu Gln Gly Arg Tyr Ile Thr Gln Asp
1220
1225
1230 Pro Met Gly Leu Lys Gly Gly Trp Asn Leu Tyr Gln Tyr Pro Leu Asn 1235 1240 1245 Pro Leu Gln Gln Ile Asp Pro Met Gly Leu Leu Gln Thr Trp Asp Asp 1250 1255 . 1260 Ala Arg Ser Gly Ala Cys Thr Gly Gly Val Cys Gly Val Leu Ser Arg 1265 1270 1275 1280 1280 Ile Ile Gly Pro Ser Lys Phe Asp Ser Thr Ala Asp Ala Ala Leu Asp 1285 1290 1295 Ala Leu Lys Glu Thr Gln Asn Arg Ser Leu Cys Asn Asp Met Glu Tyr 1300 1305 1310

Ser Gly Ile Val Cys Lys Asp Thr Asn Gly Lys Tyr Phe Ala Ser Lys 1315 1320 1325 Ala Glu Thr Asp Asn Leu Arg Lys Glu Ser Tyr Pro Leu Lys Arg Lys 1335 1340

<210> 341 <211> 122 <212> PRT <213> E. Coli

| Met | Lys | Tyr | Ser | Ser | Ile | Phe | Ser | Met | Leu | Ser | Phe | Phe | Ile | Leu | Phe | Ise | Phe | Phe | Ise | Phe | Phe | Ise | Phe | Phe | Ise | Phe | Phe | Phe | Ise | Phe | Phe

120

<210> 342 <211> 236 <212> PRT <213> E. Coli

115

 400> 342

 Met Leu Ala Leu Met Leu Met Leu Het Leu Ser Sly Ala Asp Gly Asn Ile Ala Trp Ser Gly Glu 15

 Tyr Asp Glu Trp Gly Asn Gln Leu Asn Glu Glu Asn Pro His His Leu 20

 Tyr Asp Glu Trp Gly Asn Gln Leu Asn Glu Glu Asn Pro His His Leu 20

 His Gln Pro Tyr Arg Leu Pro Gly Gln Gln Tyr Asp Lys Glu Ser Gly 40

 Leu Tyr Tyr Asn Arg Asn Arg Tyr Tyr Asp Pro Leu Gln Gly Arg Tyr 50

 Ile Thr Gln Asp Pro Ile Gly Leu Glu Gly Gly Trp Ser Leu Tyr Ala 65

 Tyr Pro Leu Asn Pro Val Asn Gly Ile Asp Pro Leu Gly Leu Ser Pro 90

 Ala Asp Val Ala Leu Ile Arg Arg Lys Asp Gln Leu Asn His Gln Arg 100

 Ala Trp Asp Ile Leu Ser Asp Thr Tyr Glu Asp Met Lys Arg Leu Asn 115

 Leu Gly Gly Thr Asp Gln Phe Phe His Cys Met Ala Phe Cys Arg Val

| 130 | 135 | 140 | 140 | 140 | 150 | 140 | 140 | 140 | 150 | 150 | 160 | 150 | 160 | 150 | 160 | 150 | 160 | 150 | 160 | 150 | 160 | 150 | 160 | 150 | 160 | 150 | 160 | 150 | 160 | 150 | 160 | 170 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175

<210> 343 <211> 86 <212> PRT <213> E. Coli

<400> 343

 Met
 Leu
 Ala
 Ile
 Ser
 Ser
 Asn
 Leu
 Ser
 Lys
 Met
 Ile
 Ile
 Ile
 Ile
 Phe
 Phe</th

<210> 344 <211> 63 <212> PRT <213> E. Coli

<400> 344

<210> 345 <211> 167 <212> PRT <213> E. Coli

<400> 345
Met Pro Gly Asn Ser Pro His Tyr Gly Arg Trp Pro Gln His Asp Phe
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Thr Ser Leu Lys Lys Leu Arg Pro Gin Ser Val Thr Ser Arg Ile Gin 20 25 Pro Gly Ser Asp Val Ile Val Cys Ala Glu Met Asp Glu Gln Trp Gly 35 40 45 Tyr Val Gly Ala Lys Ser Arg Gln Arg Trp Leu Phe Tyr Ala Tyr Asp Ser Leu Arg Lys Thr Val Val Ala His Val Phe Gly Glu Arg Thr Met 65 70 75 80 75 Ala Thr Leu Gly Arg Leu Met Ser Leu Leu Ser Pro Phe Asp Val Val 85 90 Ile Trp Met Thr Asp Gly Trp Pro Leu Tyr Glu Ser Arg Leu Lys Gly 100 105 110 Lys Leu His Val Ile Ser Lys Arg Tyr Thr Gln Arg Ile Glu Arg His 115 120 125 Asn Leu Asn Leu Arg Gln His Leu Ala Arg Leu Gly Arg Lys Ser Leu 130 135 140 140 Ser Phe Ser Lys Ser Val Glu Leu His Asp Lys Val Ile Gly His Tyr 150 Leu Asn Ile Lys His Tyr Gln 165

<210> 346 <211> 91 <212> PRT

<213> E. Coli

 Add
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 Ile
 Ser
 Cys
 Pro
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 Cys
 Ser
 Ala
 Thr
 Asp
 Gly
 Gly
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 Asp
 Gly
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 In
 In
 Asp
 Gly
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<210> 347 <211> 138 <212> PRT <213> E. Coli

 400>
 347

 Met
 Met
 Thr
 Lys
 Thr
 Gln
 Ile
 Asn
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 Lys
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 Met
 Asn
 Asp
 Asp
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Asn Glu Phe Tyr Arg Asn Asn Asp Phe Ile Asn Pro Asp Leu Gln
100 105 110 110

Glu Arg Leu Val Ile Gly Asp Tyr Ser Ile Ser Ile Phe Thr Tyr Asp
115 120 125

Ile Lys Gly Asp Ala Ala Asn Leu Leu Ile
130 135

<210> 348 <211> 392 <212> PRT <213> E. Coli

<400> 348 Ile Ser Ala Gly Cys Gly Thr Ser Glu Ser Thr Gly Asn Arg Trp Gln 20 25 30 Ser Gly His Glu Asp Glu Ile Phe Thr Phe Ser Leu Leu Asn Asn Ile 35 40 45 Asn Asn Thr Gly Leu Gly Ser Gln Phe His Gly Ile Thr Phe Cys Lys 50 60 Leu Ile Asp Lys Ser Thr Pro Leu Phe Ile Asn Ser Ile Asn Asn Asn 65 70 75 80 Glu Gln Lou Phe Met Gly Phe Asp Phe Tyr Arg Ile Asn Arg Phe Gly 85 90 95 Arg Leu Glu Lys Tyr Tyr Tyr Ile Gln Leu Arg Gly Ala Phe Leu Ser 100 105 110 Ala Ile His His Gln Ile Ile Glu Asn Gln Leu Asp Thr Glu Thr Ile
115 120 125 Thr Ile Ser Tyr Glu Phe Ile Leu Cys Gln His Leu Ile Ala Asn Thr 130 135 140 Glu Phe Ser Tyr Leu Ala Leu Pro Glu Asn Tyr Asn Arg Leu Phe Leu 145 150 155 160 Pro Asn Ser Lys Asn Gln Thr Asn Asn Arg Phe Lys Thr Leu Asn Ser 165 170 175 Lys Ala Ile Gly Arg Leu Leu Ala Ala Gly Gly Val Tyr Asn Gly Asn 180 . 185 190 Ile Glu Gly Phe Arg Asp Thr Ala Glu Lys Leu Gly Gly Asp Ala Ile
. 195 200 205 Lys Gly Tyr Asp Gln Ile Leu Asn Glu Lys Thr Ala Gly Ile Ala Ile 210 215 220 Ala Thr Ala Ser Ile Leu Leu Thr Lys Arg Ser Asn Val Asp Thr Tyr 225 230 235 240 Thr Glu Ile Asn Ser Tyr Leu Gly Lys Leu Arg Gly Gln Gln Lys Leu 245 250 255 Leu Asp Gly Ile Asp Ile Ile Glu Ile Ile Tyr Ile Lys Arg Pro Ser 260 265 270 Lys Asp Leu Ala Asn Leu Arg Lys Glu Phe Asn Lys Thr Val Arg Lys 275 280 285 Asn Phe Leu Ile Lys Leu Ala Lys Thr Ser Glu Ala Ser Gly Arg Phe 290 295 300 Asn Ala Glu Asp Leu Leu Arg Met Arg Lys Gly Asn Val Pro Leu Asn 305 310 315 320 Tyr Asn Val His His Lys Leu Ser Leu Asp Asp Gly Gly Thr Asn Asp 325 330 335 Phe Glu Asn Leu Val Leu Ile Glu Asn Glu Pro Tyr His Lys Val Phe 340 345 350 Thr Asn Met Gln Ser Arg Ile Ala Lys Gly Ile Leu Val Gly Glu Ser 355 360 365 Lys Ile Thr Pro Trp Ala Ile Pro Ser Gly Ser Ile Tyr Pro Pro Met

380

370 375 Lys Asn Ile Met Asp His Thr Lys 385 390

> <210> 349 <211> 221 <212> PRT <213> E. Coli

<400> 349 Met Val Leu Ala Leu Asn Tyr Asn Met His Gly Val Asn Ile Arg Ser 1 5 10 15 Glu Asn Ala Ala Lys Pro His Thr Met Pro Ser Arg Tyr Leu Cys Glu 20 25 30 Tyr Ile Arg Ser Ile Glu Lys Asn Gly His Ala Leu Asp Phe Gly Cys 35 40 45 Gly Lys Leu Arg Tyr Ser Asp Glu Leu Ile Ser Lys Phe Asp Glu Val Thr Phe Leu Asp Ser Lys Arg Gln Leu Glu Arg Glu Gln Ile Ile Arg 65 70 75 80 Gly Ile Lys Thr Lys Ile Ile Asp Tyr Val Pro Arg Tyr Tyr Lys Asn 85 90 95 Ala Asn Thr Val Ala Phe Glu Asp Val Asp Lys Ile Ile Gly Gly Tyr 100 105 110Asp Phe Ilc Leu Cys Scr Asn Val Leu Scr Ala Val Pro Cys Arg Asp 115 120 125 Thr Ile Asp Lys Ile Val Leu Ser Ile Lys Arg Leu Leu Lys Ser Gly 130 135 140 Gly Glu Thr Leu Ile Val Asn Gln Tyr Lys Ser Ser Tyr Phe Lys Lys 145 150 155 160 Tyr Glu Thr Gly Arg Lys His Leu Tyr Gly Tyr Ile Tyr Lys Asn Ser 165 170 175 Lys Ser Val Ser Tyr Tyr Gly Leu Leu Asp Glu Leu Ala Val Gln Glu 180 185 190 Ile Cys Ser Ser His Gly Leu Glu Ile Leu Lys Ser Trp Ser Lys Ala 195 · 200 205 Gly Ser Ser Tyr Val Thr Val Gly Ser Cys Asn Ala Ile 215

<210> 350 <211> 234 <212> PRT <213> E. Coli

 <400> 350

 Met Asn Asn Met Asn Asn Met Phe Glu Pro Solution
 Pro Lys Asn Tyr Asn Glu Met Leu Pro 15

 Lys Leu His Lys Ala Thr Phe Leu Asn Thr Leu Ile Tyr Cys Ile Leu 20
 25

 Leu Val Ile Tyr Glu Tyr Ile Pro Leu Ile Thr Leu Pro Thr Lys Tyr 35
 40

 Val Pro Pro Pro Ile Lys Asp His Glu Ser Phe Ile Asn Trp Ala Leu Ser 50
 55

 Phe Gly Ile Leu Pro Cys Ala Phe Ala Ile Phe Ala Tyr Leu Ile Ser 65
 70

 Gly Ala Leu Asp Leu His Asn Asn Ala Ala Lys Leu Leu Arg Val Arg 85
 90

 Tyr Leu Trp Asp Lys His Leu Ile Ile Lys Pro Leu Ser Arg Arg Ala

Gly Val Asn Arg Lys Leu Asn Lys Asp Glu Ala His Asn Val Met Ser 115 - 12

<210> 351 <211> 94 <212> PRT <213> E. Coli

<400> 351

 Met
 Phe
 Thr
 Ile
 Asn
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 Glu
 Val
 Arg
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 Glu
 Gly
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 Gly
 Ala

 Ser
 Arg
 Arg
 Leu
 Arg
 Ala
 Ala
 Ala
 Lys
 Phe
 Pro
 Ala
 Ile
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 Tyr
 Gly
 Sly
 Ala
 Ile
 Glu
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 Asp
 Asp

<210> 352 <211> 658 <212> PRT <213> E. Coli

 <400>
 352

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 Leu
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 Tyr
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 Ala
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 Trp
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 Asp
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 Lys
 Asn
 Asp
 Gln

 Val
 Arg
 Ile
 Met
 Asn
 Leu
 Thr
 Thr
 Leu
 Thr
 His
 Arg
 Asp
 Ala
 Leu

 Cys
 Leu
 Asn
 Ala
 Arg
 Phe
 Thr
 Se
 Arg
 Glu
 Glu
 Glu
 Ala
 Ile
 His
 Ala
 Leu

 Cys
 Leu
 Asn
 Ala
 Ala
 Leu
 Glu
 Glu
 Glu
 Ala
 Ile
 His
 Ala
 Leu
 Ala
 Ile
 His
 Ala
 Leu
 Glu
 Phe
 Ala
 Arg
 Glu
 Ser
 Ser
 Ser
 Thr
 Glu
 Fhe
 Ala
 Leu
 Glu
 Phe
 Ala
 Ile
 His
 Glu
 Ala
 Ile
 His
 Glu
 Ala
 Ile
 His
 Glu
 Ala
 Ile
 His
 Ile
 Ile
 Ile

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115
                                   120
 Asn Glu Ala Gly Thr Thr His Met Gln Leu Leu Thr Ala Leu Thr Thr
130 135 140
 Arg Leu Ala Asp Asp Glu Ile Arg Ala Arg Ile Gln Ser Ala Thr Thr 145 150 155 160
 Pro Asp Glu Leu Leu Ser Ala Leu Asp Asp Lys Gly Gly Thr Gln Pro
165 170 175
 Ser Ala Ser Phe Ser Asn Ala Pro Thr Ile Val Cys Val Thr Ala Cys
180 185 190
 Pro Ala Gly Ile Ala His Thr Tyr Met Ala Ala Glu Tyr Leu Glu Lys
195 200 205
 Ala Gly Arg Lys Leu Gly Val Asn Val Tyr Val Glu Lys Gln Gly Ala
210 215 220
 Asn Gly Ile Glu Gly Arg Leu Thr Ala Asp Gln Leu Asn Ser Ala Thr 225 230 235 240
Ala Cys Ile Phe Ala Ala Glu Val Ala Ile Lys Glu Ser Glu Arg Phe
245 250 255
Asn Gly Ile Pro Ala Leu Ser Val Pro Val Ala Glu Pro Ile Arg His 260 265 270
Ala Glu Ala Leu Ile Gln Gln Ala Leu Thr Leu Lys Arg Ser Asp Glu
275 280 285
Thr Arg Thr Val Gln Gln Asp Thr Gln Pro Val Lys Ser Val Lys Thr 290 295 300
Glu Leu Lys Gln Ala Leu Leu Ser Gly Ile Ser Phe Ala Val Pro Leu
305 310 315 320
Ile Val Ala Gly Gly Thr Val Leu Ala Val Ala Val Leu Leu Ser Gln 325 330 335
Ile Phe Gly Leu Gln Asp Leu Phe Asn Glu Glu Asn Ser Trp Leu Trp 340 345 350
Met Tyr Arg Lys Leu Gly Gly Gly Leu Leu Gly Ile Leu Met Val Pro
355 360 365
Val Leu Ala Ala Tyr Thr Ala Tyr Ser Leu Ala Asp Lys Pro Ala Leu
370 375 380
Ala Pro Gly Phe Ala Ala Gly Leu Ala Ala Asn Met Ile Gly Ser Gly 385 390 395 400
Phe Leu Gly Ala Val Val Gly Gly Leu Ile Ala Gly Tyr Leu Met Arg
405 410 415
Trp Val Lys Asn His Leu Arg Leu Ser Ser Lys Phe Asn Gly Phe Leu 420 425 430
Thr Phe Tyr Leu Tyr Pro Val Leu Gly Thr Leu Gly Ala Gly Ser Leu 435 440 445
Met Leu Phe Val Val Gly Glu Pro Val Ala Trp Ile Asn Asn Ser Leu 450 460

Thr Ala Trp Leu Asn Gly Leu Ser Gly Ser Asn Ala Leu Leu Gly 465 470 480
Ala Ile Leu Gly Phe Met Cys Ser Phe Asp Leu Gly Gly Pro Val Asn
485 490 495
Lys Ala Ala Tyr Ala Phe Cys Leu Gly Ala Met Ala Asn Gly Val Tyr 500 505 510
Gly Pro Tyr Ala Ile Phe Ala Ser Val Lys Met Val Ser Ala Phe Thr 515 525
Val Thr Ala Ser Thr Met Leu Ala Pro Arg Leu Phe Lys Glu Phe Glu
530 535 540
Ile Glu Thr Gly Lys Ser Thr Trp Leu Leu Gly Leu Ala Gly Ile Thr 545 550 560
Glu Gly Ala Ile Pro Met Ala Ile Glu Asp Pro Leu Arg Val Ile Gly
565 570 575
Ser Phe Val Leu Gly Ser Met Val Thr Gly Ala Ile Val Gly Ala Met 580 585 590
Asn Ile Gly Leu Ser Thr Pro Gly Ala Gly Ile Phe Ser Leu Phe Leu
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Leu His Asp Asn Gly Ala Gly Gly Val Met Ala Ala Ile Gly Trp Phe
610
615
620
Gly Ala Ala Leu Val Gly Ala Ala Ile Ser Thr Ala Ile Leu Leu Met
625
630
640
Trp Arg Arg His Ala Val Lys His Gly Asn Tyr Leu Thr Asp Gly Val
645
655
Met Pro

<210> 353 <211> 877 <212> PRT <213> E. Coli

<400> 353 Met Lys Ala Val Ser Arg Val His Ile Thr Pro His Met His Trp Asp 1 5 10 15 Arg Glu Trp Tyr Phe Thr Thr Glu Glu Ser Arg Ile Leu Leu Val Asn 20 25 30 As Met Glu Glu Ile Leu Cys Arg Leu Glu Gln Asp As Glu Tyr Lys 35 40 45Tyr Tyr Val Leu Asp Gly Gln Thr Ala Ile Leu Glu Asp Tyr Phe Ala 50 55 60 Val Lys Pro Glu Asn Lys Asp Arg Val Lys Lys Gln Val Glu Ala Gly 70 75 80 Lys Leu Ile Ile Gly Pro Trp Tyr Thr Gln Thr Asp Thr Thr Ile Val 85 90 95 Ser Ala Glu Ser Ile Val Arg Asn Leu Met Tyr Gly Met Arg Asp Cys 100 105 110 Leu Ala Phe Gly Glu Pro Met Lys Ile Gly Tyr Leu Pro Asp Ser Phe 115 120 125 Gly Met Ser Gly Gln Leu Pro His Ile Tyr Asn Gly Phe Gly Ile Thr 130 135 140 Arg Thr Met Phe Trp Arg Gly Cys Ser Glu Arg His Gly Thr Asp Lys 145 150 155 160 Thr Glu Phe Leu Trp Gln Ser Ser Asp Gly Ser Glu Val Thr Ala Gln 165 170 175Val Leu Pro Leu Gly Tyr Ala Ile Gly Lys Tyr Leu Pro Ala Asp Glu 180 185 190 Asn Gly Leu Arg Lys Arg Leu Asp Ser Tyr Phe Asp Val Leu Glu Lys Ala Ser Val Thr Lys Glu Ile Leu Leu Pro Asn Gly His Asp Gln Met 210 215 220 Pro Leu Gln Gln Asn Ile Phe Glu Val Met Asp Lys Leu Arg Glu Ile 225 230 235 240 Tyr Pro Gln Arg Lys Phe Val Met Ser Arg Phe Glu Glu Val Phe Glu 245 250 255 Lys Ile Glu Ala Gln Arg Asp Asn Leu Ala Thr Leu Lys Gly Glu Phe 260 265 270 Ile Asp Gly Lys Tyr Met Arg Val His Arg Thr Ile Gly Ser Thr Arg 275 280 285 Met Asp Ile Lys Ile Ala His Ala Arg Ile Glu Asn Lys Ile Val Asn 290 295 300 Leu Leu Glu Pro Leu Ala Thr Leu Ala Trp Thr Leu Gly Phe Glu Tyr 305 310 315 320 His His Gly Leu Leu Glu Lys Met Trp Lys Glu Ile Leu Lys Asn His 325 330 335 Ala His Asp Ser Ile Gly Cys Cys Cys Ser Asp Lys Val His Arg Glu 340 345 350 Ile Val Ala Arg Phe Glu Leu Ala Glu Asp Met Ala Asp Asn Leu Ile

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355
                                  360
 Arg Phe Tyr Met Arg Lys Ile Ala Asp Asn Met Pro Gln Ser Asp Ala
370 375 380
 Asp Lys Leu Val Leu Phe Asn Leu Met Pro Trp Pro Arg Glu Glu Val
385 390 395 400
 Ile Asn Thr Thr Val Arg Leu Arg Ala Ser Gln Phe Asn Leu Arg Asp
405 410 415 .
 Asp Arg Gly Gln Pro Val Pro Tyr Phe Ile Arg His Ala Arg Glu Ile
420 425 430
 Asp Pro Gly Leu Ile Asp Arg Gln Ile Val His Tyr Gly Asn Tyr Asp
435 440 445
 Pro Phe Met Glu Phe Asp Ile Gln Ile Asn Gln Ile Val Pro Ser Met 450 455 460
Gly Tyr Arg Thr Leu Tyr Ile Glu Ala Asn Gin Pro Gly Asn Val Ile
465 470 475 480
 Ala Ala Lys Ser Asp Ala Glu Gly Ile Leu Glu Asn Ala Phe Trp Gln
485 490 495
 Ile Ala Leu Asn Glu Asp Gly Ser Leu Gln Leu Val Asp Lys Asp Ser 500 505 510
Gly Val Arg Tyr Asp Arg Val Leu Gln Ile Glu Glu Ser Ser Asp Asp
515 520 525
Gly Asp Glu Tyr Asp Tyr Ser Pro Ala Lys Glu Glu Trp Val Ile Thr
530 535 540
Ala Ala Asn Ala Lys Pro Gln Cys Asp Ile Ile His Glu Ala Trp Gln 545 550 555 560
Ser Arg Ala Val Ile Arg Tyr Asp Met Ala Val Pro Leu Asn Leu Ser
565 570 575
Glu Arg Ser Ala Arg Gln Ser Thr Gly Arg Val Gly Val Val Leu Val 580 585 590
Val Thr Leu Ser His Asn Ser Arg Arg Ile Asp Val Asp Ile Asn Leu 595 600 605
Asp Asn Gln Ala Asp Asp His Arg Leu Arg Val Leu Val Pro Thr Pro 610 615 620
Phe Asn Thr Asp Ser Val Leu Ala Asp Thr Gln Phe Gly Ser Leu Thr 625 630 635 640
Arg Pro Val Asn Asp Ser Ala Met Asn Asn Trp Gln Gln Glu Gly Trp
645 650 655
Lys Glu Ala Pro Val Pro Val Trp Asn Met Leu Asn Tyr Val Ala Leu
660 665 670
Gln Glu Gly Arg Asn Gly Met Ala Val Phe Ser Glu Gly Leu Arg Glu
675 680 685
Phe Glu Val Ile Gly Glu Glu Lys Lys Thr Phe Ala Ile Thr Leu Leu 690 695 700
Arg Gly Val Gly Leu Leu Gly Lys Glu Asp Leu Leu Leu Arg Pro Gly 705 710 715 720
Arg Pro Ser Gly Ile Lys Met Pro Val Pro Asp Ser Gln Leu Arg Gly
725 730 735
Leu Leu Ser Cys Arg Leu Ser Leu Leu Ser Tyr Thr Gly Thr Pro Thr 740 745 750
Ala Ala Gly Val Ala Gln Gln Ala Arg Ala Trp Leu Thr Pro Val Gln 755 760 765
Cys Tyr Asn Lys Ile Pro Trp Asp Val Met Lys Leu Asn Lys Ala Gly 770 780
Phe Asn Val Pro Glu Ser Tyr Ser Leu Leu Lys Met Pro Pro Val Gly 785 790 795 800
Cys Leu Ile Scr Ala Leu Lys Lys Ala Glu Asp Arg Gln Glu Val Ile
805 810 815
Leu Arg Leu Phe Asn Pro Ala Glu Ser Ala Thr Cys Asp Ala Thr Val
820 825 830
Ala Phe Ser Arg Glu Val Ile Ser Cys Ser Glu Thr Met Met Asp Glu
                                 840
                                                         845
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His Ile Thr Thr Glu Glu Asn Gln Gly Ser Asn Leu Ser Gly Pro Phe 850 855 860 Leu Pro Gly Gln Ser Arg Thr Phe Ser Tyr Arg Leu Ala 865 870 875

<210> 354 <211> 523 <212> PRT <213> E. Coli

<400> 354 Met Met Leu Asp Ile Val Glu Leu Ser Arg Leu Gln Phe Ala Leu Thr 1 5 10 15 Ala Met Tyr His Phe Leu Phe Val Pro Leu Thr Leu Gly Met Ala Phe 20 25 30 Leu Leu Ala Ile Met Glu Thr Val Tyr Val Leu Ser Gly Lys Gln Ile 35 40 45 Tyr Lys Asp Met Thr Lys Phe Trp Gly Lys Leu Phe Gly Ile Asn Phe 50 60 Ala Leu Gly Val Ala Thr Gly Leu Thr Met Glu Phe Gln Phe Gly Thr 65 70 75 80 Asn Trp Ser Tyr Tyr Ser His Tyr Val Gly Asp Ile Phe Gly Ala Pro Leu Ala Ile Glu Gly Leu Met Ala Phe Phe Leu Glu Ser Thr Phe Val Gly Leu Phe Phe Phe Gly Trp Asp Arg Leu Gly Lys Val Gln His Met Cys Val Thr Trp Leu Val Ala Leu Gly Ser Asn Leu Ser Ala Leu Trp
130 135 140 Ile Leu Val Ala Asn Gly Trp Met Gln Asn Pro Ile Ala Ser Asp Phe 145 . 150 155 160 Asn Phe Glu Thr Met Arg Met Glu Met Val Ser Phe Ser Glu Leu Val 165 170 175 Leu Asn Pro Val Ala Gln Val Lys Phe Val His Thr Val Ala Ser Gly 180 185 190 Tyr Val Thr Gly Ala Met Phe Ile Leu Gly Ile Ser Ala Trp Tyr Met 195 200 205 Leu Lys Gly Arg Asp Phe Ala Phe Ala Lys Arg Ser Phe Ala Ile Ala 210 215 220 Ala Ser Phe Gly Met Ala Ala Val Leu Ser Val Ile Val Leu Gly Asp 225 230 235 240 Glu Ser Gly Tyr Glu Met Gly Asp Val Gln Lys Thr Lys Leu Ala Ala 245 250 255 Ile Glu Ala Glu Trp Glu Thr Gln Pro Ala Pro Ala Ala Phe Thr Leu 260 265 270 Phe Gly Ile Pro Asp Gln Glu Glu Glu Thr Asn Lys Phe Ala Ile Gln 275 280 285 285 Ile Pro Tyr Ala Leu Gly Ile Ile Ala Thr Arg Ser Val Asp Thr Pro 290 295 300 Val Ile Gly Leu Lys Glu Leu Met Val Gln His Glu Glu Arg Ile Arg 305 310 315 320 Asn Gly Met Lys Ala Tyr Ser Leu Leu Glu Gln Leu Arg Ser Gly Ser 325 330 335 Thr Asp Gln Ala Val Arg Asp Gln Phe Asn Ser Met Lys Lys Asp Leu 340 345 350 Gly Tyr Gly Leu Leu Lys Arg Tyr Thr Pro Asn Val Ala Asp Ala 355 360 365 Thr Glu Ala Gln Ile Gln Gln Ala Thr Lys Asp Ser Ile Pro Arg Val 370 375 380 Ala Pro Leu Tyr Phe Ala Phe Arg Ile Met Val Ala Cys Gly Phe Leu

<210> 355 <211> 379 <212> PRT <213> E. Coli

<400> 355 Met Ile Asp Tyr Glu Val Leu Arg Phe Ile Trp Trp Leu Leu Val Gly 10 Val Leu Leu Ile Gly Phe Ala Val Thr Asp Gly Phe Asp Met Gly Val 20 25 30 Gly Met Leu Thr Arg Phe Leu Gly Arg Asn Asp Thr Glu Arg Arg Ile $35 \ \ \, 40 \ \ \, 45$ Met Ile Asn Ser Ile Ala Pro His Trp Asp Gly Asn Gln Val Trp Leu 50 55 60 Ile Thr Ala Gly Gly Ala Leu Phe Ala Ala Trp Pro Met Val Tyr Ala 65 70 75 80 Ala Ala Phe Ser Gly Phe Tyr Val Ala Met Ile Leu Val Leu Ala Ser 85 90 95 Leu Phe Phe Arg Pro Val Gly Phe Asp Tyr Arg Ser Lys Ile Glu Glu 100 105 110 Thr Arg Trp Arg Asn Met Trp Asp Trp Gly Ile Phe Ile Gly Ser Phe
115 120 125 Val Pro Pro Leu Val Ile Gly Val Ala Phe Gly Asn Leu Leu Gln Gly 130 135 140 Val Pro Phe Asn Val Asp Glu Tyr Leu Arg Leu Tyr Tyr Thr Gly Asn 145 150 155 160 Phe Phe Gln Leu Leu Asn Pro Phe Gly Leu Leu Ala Gly Val Val Ser 165 170 175 Val Gly Met Ile Ile Thr Gln Gly Ala Thr Tyr Leu Gln Met Arg Thr 180 185 190 Val Gly Glu Leu His Leu Arg Thr Arg Ala Thr Ala Gln Val Ala Ala 195 200 205 Leu Val Thr Leu Val Cys Phe Ala Leu Ala Gly Val Trp Val Met Tyr 210 215 220 Gly Ile Asp Gly Tyr Val Val Lys Ser Thr Met Asp His Tyr Ala Ala 225 230 235 240 Ser Asn Pro Leu Asn Lys Glu Val Val Arg Glu Ala Gly Ala Trp Leu 245 250 255 Val Asn Phé Asn Asn Thr Pro Ile Leu Trp Ala Ile Pro Ala Leu Gly 260 265 270 Val Val Leu Pro Leu Leu Thr Ile Leu Thr Ala Arg Met Asp Lys Ala 275 280 285

<210> 356 <211> 456 <212> PRT <213> E. Coli

<400> 356 Met Glu Leu Ser Ser Leu Thr Ala Val Ser Pro Val Asp Gly Arg Tyr 5 10 Gly Asp Lys Val Ser Ala Leu Arg Gly Ile Phe Ser Glu Tyr Gly Leu 20 25 30 Leu Lys Phe Arg Val Gln Val Glu Val Arg Trp Leu Gln Lys Leu Ala $35 \hspace{1.5cm} 40 \hspace{1.5cm} 45$ Ala His Ala Ala Ile Lys Glu Val Pro Ala Phe Ala Ala Asp Ala Ile 50 55 60 Gly Tyr Leu Asp Ala Ile Val Ala Ser Phe Ser Glu Glu Asp Ala Ala 65 70 75 80 Arg Ile Lys Thr Ile Glu Arg Thr Thr Asn His Asp Val Lys Ala Val 85 90 95 Glu Tyr Phe Leu Lys Glu Lys Val Ala Glu Ile Pro Glu Leu His Ala 100 105 110 Val Ser Glu Phe Ile His Phe Ala Cys Thr Ser Glu Asp Ile Asn Asn 115 120 125 Leu Ser His Ala Leu Met Leu Lys Thr Ala Arg Asp Glu Val Ile Leu 130 135 140 Pro Tyr Trp Arg Gln Leu Ile Asp Gly Ile Lys Asp Leu Ala Val Gln 145 150 155 160 Tyr Arg Asp Ile Pro Leu Leu Ser Arg Thr His Gly Gln Pro Ala Thr 165 170 175 Pro Ser Thr Ile Gly Lys Glu Met Ala Asn Val Ala Tyr Arg Met Glu 180 185 190 Arg Gln Tyr Arg Gln Leu Asn Gln Val Glu Ile Leu Gly Lys Ile Asn 195 200 205 Gly Ala Val Gly Asn Tyr Asn Ala His Ile Ala Ala Tyr Pro Glu Val 210 215 220 Asp Trp His Gln Phe Ser Glu Glu Phe Val Thr Ser Leu Gly Ile Gln 225 230 235 240 Trp Asn Pro Tyr Thr Thr Gln Ile Glu Pro His Asp Tyr Ile Ala Glu 245 250 255 Leu Phe Asp Cys Val Ala Arg Phe Asn Thr Ile Leu Ile Asp Phe Asp 260 265 270 Arg Asp Val Trp Gly Tyr Ile Ala Leu Asn His Phe Lys Gln Lys Thr 275 280 285 Ile Ala Gly Glu Ile Gly Ser Ser Thr Met Pro His Lys Val Asn Pro 290 295 300 Ile Asp Phe Glu Asn Ser Glu Gly Asn Leu Gly Leu Ser Asn Ala Val 305 310 315 320 Leu Gln His Leu Ala Ser Lys Leu Pro Val Ser Arg Trp Gln Arg Asp

```
330
Leu Thr Asp Ser Thr Val Leu Arg Asn Leu Gly Val Gly Ile Gly Tyr 340 345 350
Ala Leu Ile Ala Tyr Gln Ser Thr Leu Lys Gly Val Ser Lys Leu Glu
355 360 365
Val Asn Arg Asp His Leu Leu Asp Glu Leu Asp His Asn Trp Glu Val
370 375 380
                                              380
Leu Ala Glu Pro Ile Gln Thr Val Met Arg Arg Tyr Gly Ile Glu Lys
385 390 395 400
                                       395
Pro Tyr Glu Lys Leu Lys Glu Leu Thr Arg Gly Lys Arg Val Asp Ala
405 410 415
Glu Gly Met Lys Gln Phe Ile Asp Gly Leu Ala Leu Pro Glu Glu Glu 420 425 430
Lys Ala Arg Leu Lys Ala Met Thr Pro Ala Asn Tyr Ile Gly Arg Ala
       435
                           440
Ile Thr Met Val Asp Glu Leu Lys
    450
                         455
      <210> 357
      <211> 61
      <212> PRT
      <213> E. Coli
      <400> 357
Met Leu Ile Leu Thr Arg Arg Val Gly Glu Thr Leu Met Ile Gly Asp
                 5
                                     10
Glu Val Thr Val Thr Val Leu Gly Val Lys Gly Asn Gln Val Arg Ile
20 25 30
Gly Val Asn Ala Pro Lys Glu Val Ser Val His Arg Glu Glu Ile Tyr
     35
                          40
Gln Arg Ile Gln Ala Glu Lys Ser Gln Gln Ser Ser Tyr
      <210> 358
      <211> 83
      <212> RNA
      <213> E. Coli
      <400> 358
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ggugaggugg ccgagaggcu gaaggcgcuc cccugcuaag ggaguaugcg gucaaaagcu

83

<210> 359 <211> 200 <212> PRT <213> E. Coli

<400> 359

 Meu Lys
 Asn-Lys
 Ala Asp Asn Lys
 Lys
 Arg Asn Phe Leu
 Leu Thr His Ser 15

 Glu Ile
 Glu Ser Leu Leu Lys
 Ala Ala Asn Thr Gly Pro His Ala Ala Ala 25
 30

 Arg Asn Tyr Cys
 Leu Thr Leu Leu Cys Phe Ile His Gly Phe Arg Ala 35
 40

 Ser Glu Ile Cys
 Arg Leu Arg Ile Ser Asp Ile Asp Leu Lys Ala Lys 50

 Cys
 Ile Tyr Ile His Arg Leu Lys Lys Lys Gly Phe Ser Thr Thr His Pro 65

 Leu Leu Asn Lys
 Glu Val Gln Ala Leu Lys
 Asn Trp Leu Ser
 11e Arg 95

 Thr Ser Tyr
 Pro His Ala Glu Ser Glu Trp Val Phe Leu Ser Arg Lys 100
 105
 110

 Gly Asn Pro Leu Ser Arg Gln Gln Phe 120
 11c Ite Ser Thr Ser 125

 Gly Gly Asn Ala Gly Leu Ser Leu Glu Ite His Pro His Met Leu Arg 130
 135
 140

 His Ser Cys Gly Phe Ala Leu Ala Asn Met Gly Ite Asp Thr Arg Leu 145
 150
 150

 Ite Gln Asp Tyr Leu Gly His Arg Asn Ite Arg His Thr Val Trp Tyr 165
 170
 170

 Thr Ala Ser Asn Ala Gly Arg Phe 180
 185
 190

 Gly Arg Gln Arg His Ala Val Leu 195
 160

<210> 360 <211> 198 <212> PRT <213> E. Coli

<210> 361 <211> 182 <212> PRT <213> E. Coli

195

<400> 361
Met Lys Ile Lys Thr Leu Ala Ile Val Val Leu Ser Ala Leu Ser Leu
1 5 10 15

Ser Ser Thr Ala Ala Leu Ala Ala Ala Thr Thr Val Asn Gly Gly Thr 20 . 25 30 Val His 'Phe Lys Gly Glu Val Val Asn Ala Ala Cys Ala Val Asp Ala 35 40 45 Gly Ser Val Asp Gln Thr Val Gln Leu Gly Gln Val Arg Thr Ala Ser 50 55 60 Leu Ala Gln Glu Gly Ala Thr Ser Ser Ala Val Gly Phe Asn Ile Gln 65 70 75 .80 Leu Asn Asp Cys Asp Thr Asn Val Ala Ser Lys Ala Ala Val Ala Phe 85 90 95 Leu Gly Thr Ala Ile Asp Ala Gly His Thr Asn Val Leu Ala Leu Gln
100 105 110 Ser Ser Ala Ala Gly Ser Ala Thr Asn Val Gly Val Gln Ile Leu Asp 115 120 125 Arg Thr Gly Ala Ala Leu Thr Leu Asp Gly Ala Thr Phe Ser Ser Glu 130 135 140 Thr Thr Leu Asn Asn Gly Thr Asn Thr Ile Pro Phe Gln Ala Arg Tyr 145 150 155 160 Phe Ala Thr Gly Ala Ala Thr Pro Gly Ala Ala Asn Ala Asp Ala Thr 165 170 Phe Lys Val Gln Tyr Gln 180

<210> 362 <211> 215 <212> PRT <213> E. Coli

210

<400> 362 Met Leu Leu Met Arg Met Arg Pro Ser Arg Phe Ser Ile Asn Asn Leu 10 Pro Arg Phe Arg Asp Val Ile Thr Gly Arg Asp Ala His Pro Cys Ala 20 25 30 Ile Lys Ile Thr Met Lys Arg Lys Arg Leu Phe Leu Leu Ala Ser Leu 35 40 45 Leu Pro Met Phe Ala Leu Ala Gly Asn Lys Trp Asn Thr Thr Leu Pro 50 . 55 60 Gly Gly Asn Met Gln Phe Gln Gly Val Ile Ile Ala Glu Thr Cys Arg 65 70 75 80 Ile Glu Ala Gly Asp Lys Gln Met Thr Val Asn Met Gly Gln Ile Ser 85 90 95 Ser Asn Arg Phe His Ala Val Gly Glu Asp Ser Ala Pro Val Pro Phe 100 105 110 Val Ile His Leu Arg Glu Cys Ser Thr Val Val Ser Glu Arg Val Gly 115 120 125 Val Ala Phe His Gly Val Ala Asp Gly Lys Asn Pro Asp Val Leu Ser 130 135 140 Val Gly Glu Gly Pro Gly Ile Ala Thr Asn Ile Gly Val Ala Leu Phe 145 150 150 160 Asp Asp Glu Gly Asn Leu Val Pro Ile Asn Arg Pro Pro Ala Asn Trp 165 170 175 Lys Arg Leu Tyr Ser Gly Ser Thr Ser Leu His Phe Ile Ala Lys Tyr 180 185 190 Arg Ala Thr Gly Arg Arg Val Thr Gly Gly Ile Ala Asn Ala Gln Ala 195 200 Trp Phe Ser Leu Thr Tyr Gln

<210> 363 <211> 241 <212> PRT <213> E. Coli

<400> 363 Met Ser Asn Lys Asn Val Asn Val Arg Lys Ser Gln Glu Ile Thr Phe 1 5 10 15 Cys Leu Leu Ala Gly Ile Leu Met Phe Met Ala Met Met Val Ala Gly 25 Arg Ala Glu Ala Gly Val Ala Leu Gly Ala Thr Arg Val Ile Tyr Pro $35 \hspace{1cm} 40 \hspace{1cm} 45$ Ala Gly Gln Lys Gln Glu Gln Leu Ala Val Thr Asn Asn Asp Glu Asn 50 60 Ser Thr Tyr Leu Ile Gln Ser Trp Val Glu Asn Ala Asp Gly Val Lys 70 75 80 Asp Gly Arg Phe Ile Val Thr Pro Pro Leu Phe Ala Met Lys Gly Lys 85 90 95 Lys Glu Asn Thr Leu Arg Ile Leu Asp Ala Thr Asn Asn Gln Leu Pro
100 105 110 Gln Asp Arg Glu Ser Leu Phe Trp Met Asn Val Lys Ala Ile Pro Ser 115 120 125 Met Asp Lys Ser Lys Leu Thr Glu Asn Thr Leu Gln Leu Ala Ile Ile 130 135 140 Ser Arg Ile Lys Leu Tyr Tyr Arg Pro Ala Lys Leu Ala Leu Pro Pro 145 150 155 160 145 Asp Gln Ala Ala Glu Lys Leu Arg Phe Arg Arg Ser Ala Asn Ser Leu 165 170 175 Thr Leu Ile Asn Pro Thr Pro Tyr Tyr Leu Thr Val Thr Glu Leu Asn 180 185 190 Ala Gly Thr Arg Val Leu Glu Asn Ala Leu Val Pro Pro Met Gly Glu 195 200 205 Ser Thr Val Lys Leu Pro Ser Asp Ala Gly Ser Asn Ile Thr Tyr Arg 210 215 220 Thr Ile Asn Asp Tyr Gly Ala Leu Thr Pro Lys Met Thr Gly Val Met 225

<210> 364 <211> 878 <212> PRT <213> E. Coli

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                                                         125
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130 135 140
Ala Thr Ala His Leu Asp Val Gly Gln Gln Arg Leu Asn Leu Thr Ile
145 150 155 160
Pro Gln Ala Phe Met Ser Asn Arg Ala Arg Gly Tyr Ile Pro Pro Glu
165 170 175
Leu Trp Asp Pro Gly Ile Asn Ala Gly Leu Leu Asn Tyr Asn Phe Ser
180 185 190
Gly Asn Ser Val Gln Asn Arg Ile Gly Gly Asn Ser His Tyr Ala Tyr
195 200 205
Leu Asn Leu Gln Ser Gly Leu Asn Ile Gly Ala Trp Arg Leu Arg Asp
210 215 220
Asn Thr Thr Trp Ser Tyr Asn Ser Ser Asp Arg Ser Ser Gly Ser Lys
225 230 235 240
Asn Lys Trp Gln His Ile Asn Thr Trp Leu Glu Arg Asp Ile Ile Pro
245 250 255
Leu Arg Ser Arg Leu Thr Leu Gly Asp Gly Tyr Thr Gln Gly Asp Ile
260 265 270
Phe Asp Gly Ile Asn Phe Arg Gly Ala Gln Leu Ala Ser Asp Asp Asn 275 280 285
Met Leu Pro Asp Ser Gln Arg Gly Phe Ala Pro Val Ile His Gly Ile
290 295 300
Ala Arg Gly Thr Ala Gln Val Thr Ile Lys Gln Asn Gly Tyr Asp Ile
305 310 315 320
Tyr Asn Ser Thr Val Pro Pro Gly Pro Phe Thr Ile Asn Asp Ile Tyr
325 330 335
Ala Ala Gly Asn Ser Gly Asp Leu Gln Val Thr Ile Lys Glu Ala Asp 340 345 350
Gly Ser Thr Gln Ile Phe Thr Val Pro Tyr Ser Ser Val Pro Leu Leu
355 360 365
Gln Arg Glu Gly His Thr Arg Tyr Ser Ile Thr Ala Gly Glu Tyr Arg
370 375 380
Ser Gly Asn Ala Gln Gln Glu Lys Thr Arg Phe Phe Gln Ser Thr Leu
385 390 395 400
Leu His Gly Leu Pro Ala Gly Trp Thr Ile Tyr Gly Gly Thr Gln Leu 405 410 415
Ala Asp Arg Tyr Arg Ala Phe Asn Phe Gly Ile Gly Lys Asn Met Gly 420 425 430
Ala Leu Gly Ala Leu Ser Val Asp Met Thr Gln Ala Asn Ser Thr Leu 435 440 445
Pro Asp Asp Ser Gln His Asp Gly Gln Ser Val Arg Phe Leu Tyr Asn 450 455 460
Lys Ser Leu Asn Glu Ser Gly Thr Asn Ile Gln Leu Val Gly Tyr Arg
465 470 475 480
Tyr Ser Thr Ser Gly Tyr Phe Asn Phe Ala Asp Thr Thr Tyr Ser Arg
485 490 495
Met Asn Gly Tyr Asn Ile Glu Thr Gln Asp Gly Val Ile Gln Val Lys
500 505 510
Pro Lys Phe Thr Asp Tyr Tyr Asn Leu Ala Tyr Asn Lys Arg Gly Lys 515 520 525
Leu Gln Leu Thr Val Thr Gln Gln Leu Gly Arg Thr Ser Thr Leu Tyr 530 535 540
Leu Ser Gly Ser His Gln Thr Tyr Trp Gly Thr Ser Asn Val Asp Glu
545 550 555 560
Gln Phe Gln Ala Gly Leu Asn Thr Ala Phe Glu Asp Ile Asn Trp Thr
565 570 575
Leu Ser Tyr Ser Leu Thr Lys Asn Ala Trp Gln Lys Gly Arg Asp Gln
580 585 590
Met Leu Ala Leu Asn Val Asn Ile Pro Phe Ser His Trp Leu Arg Ser
                               600
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Asp Ser Lys Ser Gln Trp Arg His Ala Ser Ala Ser Tyr Ser Met Ser 610 615 620 His Asp Leu Asn Gly Arg Met Thr Asn Leu Ala Gly Val Tyr Gly Thr 625 630 635 640 Leu Leu Glu Asp Asn Asn Leu Ser Tyr Ser Val Gln Thr Gly Tyr Ala
645
650
655
Gly Gly Gly Asp Gly Asn Ser Gly Ser Thr Gly Tyr Ala Thr Leu Asn
660
665
670 Tyr Arg Gly Gly Tyr Gly Asn Ala Asn Ile Gly Tyr Ser His Ser Asp 675 685 Asp Tie Lys Gln Leu Tyr Tyr Gly Val Ser Gly Gly Val Leu Ala His 690 695 700 Ala Asn Gly Val Thr Leu Gly Gln Pro Leu Asn Asp Thr Val Val Leu 705 710 715 720 Val Lys Ala Pro Gly Ala Lys Asp Ala Lys Val Glu Asn Gln Thr Gly
725 730 735 Val Arg Thr Asp Trp Arg Gly Tyr Ala Val Leu Pro Tyr Ala Thr Glu 740 745 750 Tyr Arg Glu Asn Arg Val Ala Leu Asp Thr Asn Thr Leu Ala Asp Asn 755 760 765 Val Asp Leu Asp Asn Ala Val Ala Asn Val Val Pro Thr Arg Gly Ala 770 780 Ile Val Arg Ala Glu Phe Lys Ala Arg Val Gly Ile Lys Leu Leu Met 785 790 795 800 Thr Leu Thr His Asn Asn Lys Pro Leu Pro Phe Gly Ala Met Val Thr 805 815 Ser-Glu Ser Ser Gln Ser Ser Gly Ilc Val Ala Asp Asn Gly Gln Val 820 825 830 Tyr Leu Ser Gly Met Pro Leu Ala Gly Lys Val Gln Val Lys Trp Gly 835 840 845 Glu Glu Glu Asn Ala His Cys Val Ala Asn Tyr Gln Leu Pro Pro Glu 850 855 860 Ser Gln Gln Gln Leu Leu Thr Gln Leu Ser Ala Glu Cys Arg 870 875

> <210> 365 <211> 176 <212> PRT <213> E. Coli

145 150 155 160
Thr Ala Gly His Ile Asn Ala Thr Ala Thr Phe Thr Leu Glu Tyr Gln
165 170 175

<210> 366 <211> 167 <212> PRT <213> E. Coli

 Ket
 Lys
 Trp
 Cys
 Lys
 Arg
 Gly
 Tyr
 Val
 Leu
 Ala
 Ala
 Ala
 Leu
 Ala
 Ala
 Ala
 Leu
 Ala
 Ala
 Ala
 Leu
 Ala
 A

<210> 367 <211> 300 <212> PRT <213> E. Coli

165

 400> 367

 Met
 Lys
 Arg
 Val
 1le
 Thr
 Leu
 Phe
 Ala
 Val
 Leu
 Leu
 Met
 Gly
 Trp
 Ser

 Val
 Asn
 Ala
 Trp
 Ser
 Phe
 Ala
 Cys
 Lys
 Thr
 Ala
 Asn
 Gly
 Thr
 Ala
 Ile
 Jie
 Jie

 Ser Leu
 Leu
 Ile
 Leu
 Ile
 Leu
 Arg
 Gln
 Thr
 Asn
 Asn
 Tyr
 Asn
 Ser
 160

 Asp
 Asp
 Phe
 Gln
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 Val
 Trp
 Asp
 Ile
 Tyr
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<210> 368 <211> 521 <212> PRT <213> E. Coli

<400> 368 Met Leu Ser Lys Leu Pro Arg Arg Leu Arg Ser Phe Gln Thr Tyr Cys $1 \hspace{1cm} 5 \hspace{1cm} 10 \hspace{1cm} 15$ Thr Ile Arg Val His Arg Gly Glu Asp Met Lys Ser Met Asp Lys Leu 20 25 30 Thr Thr Gly Val Ala Tyr Gly Thr Ser Ala Gly Asn Ala Gly Phe Trp 35 40 45 Ala Leu Gln Leu Leu Asp Lys Val Thr Pro Ser Gln Trp Ala Ala Ile 50 55 60 Gly Val Leu Gly Ser Leu Val Phe Gly Leu Leu Thr Tyr Leu Thr Asn 65 70 75 80 Leu Tyr Phe Lys Ile Lys Glu Asp Arg Arg Lys Ala Ala Arg Gly Glu 85 90 95 Ser Asn Asp Ser Arg Leu Thr Gly Cys Glu Arg Ser Pro Phe Glu Ser 100 105 110 Tyr Gly Asn Cys Ser Leu Thr Gly Gln Arg Thr Leu Arg Asn Phe Pro 115 120 125 Gly Cys Arg His Gly Pro Cys Arg Ser Cys Ala Gly Val Leu Gly Ser 130 135 140 Ser Gln Lys Glu Arg Pro Ala Ser Leu Pro Gly Ser Ser Arg Lys Ile 145 150 155 160 Val Arg Lys Ser Val Leu Ser Ala Ala Ser Val Leu Leu Asp Lys Ser 165 170 175 Cys Gln Ala Arg Ala Ser Ser Ser Ile Ser Met Asn Thr Lys Ile Arg 180 185 190 Tyr Gly Leu Ser Ala Ala Val Leu Ala Leu Ile Gly Ala Gly Ala Ser 195 200 205 Ala Pro Gln Ile Leu Asp Gln Phe Leu Asp Glu Lys Glu Gly Asn His 210 215 220 Thr Met Ala Tyr Arg Asp Gly Ser Gly Ile Trp Thr Ile Cys Arg Gly 225 230 235 240 Ala Thr Val Val Asp Gly Lys Thr Val Phe Pro Asn Met Lys Leu Ser 250

Lys Glu Lys Cys Asp Gln Val Asn Ala Ilc Glu Arg Asp Lys Ala Leu 260 265 270 265 Ala Trp Val Glu Arg Asn Ile Lys Val Pro Leu Thr Glu Pro Gln Lys 275 280 285 Ala Gly Ile Ala Ser Phe Cys Pro Tyr Asn Ile Gly Pro Gly Lys Cys 290 295 300 Phe Pro Ser Thr Phe Tyr Lys Arg Leu Asn Ala Gly Asp Arg Lys Gly 305 310 315 320 Ala Cys Glu Ala Ile Arg Trp Trp Ile Lys Asp Gly Gly Arg Asp Cys 325 330 335 Arg Ile Arg Ser Asn Asn Cys Tyr Gly Gln Val Ile Arg Arg Asp Gln 340 345 350 Glu Ser Ala Leu Thr Cys Trp Gly Ile Glu Gln Ile Arg Tyr Ser Trp 355 360 365 Phe Phe Ser Cys Cys Gln Asp Leu Ser Ser Glu Met Ser Gly Ala Thr 370 375 380 Glu Asp Gly Lys Lys Asn Gly Arg Asn Val Met Leu Pro His Tyr His 385 390 395 400 Lys Arg Met Leu Asn Leu Leu Clu Leu Asn Arg Gly Glu Leu Pro 405 410 415 Val Met Arg Leu Leu Lys Met Arg Asn Arg Asn Leu Leu Lys Phe Leu 420 425 430 Pro Gly Leu Leu Ile Cys Leu Ile Val Leu Thr Ser Cys Val Pro Lys 435 440 445 Gln Lys Asn Met Pro Tyr Ala Leu Thr Gln Arg Ser Ile Pro Gln Ile 450 455 460 Leu Pro Leu Pro Ser Glu Ala Lys Gln Pro Lys Pro Pro Lys Glu Cys 465 470 475 480 Ser Pro Thr Cys Ser Glu Ile Leu Gln Gln Lys Leu Ser Phe Met Leu 485 490 495 Lys Leu Leu Thr Asn Ala Thr Ser Gln Glu Leu Val Asn Arg Ser Met 500 505 510 500 Asn Leu Glu Ile Lys Ser Ile Lys Cys 515

<210> 369 <211> 177 <212> PRT <213> E. Coli

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 Asn
 Thr
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 Ala
 Ala
 Leu
 Asp
 Gln
 Gln
 Phe
 Leu
 Asp
 Gln
 Phe
 Leu
 Asp
 Gln
 Ile
 Ala
 Ala
 Tyr
 Arg
 Asp
 Gln
 Ile
 Asp
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 Ile
 Ala
 Ile
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Asp Gly Gly Arg Asp Cys Arg Ile Arg Ser Asn Asn Cys Tyr Gly Gln
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Val Ile Arg Arg Asp Gln Glu Ser Ala Leu Thr Cys Trp Gly Ile Glu
165 170 175

<210> 370 <211> 103 <212> PRT <213> E. Coli

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 Thr
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 Asp
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 Glu
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 Asn
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 Val
 Thr
 Val
 Ala
 Leu
 Gln
 Asp
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 Asp
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 Asp
 Asp
 Asp
 Asp
 Asp
 Leu
 Asp
 Asp</t

<210> 371 <211> 96 <212> PRT <213> E. Coli

Met	Leu	Ser	Lys	Leu	Pro	Arg	Arg	Leu	Arg	Ser	Phe	Gln	Thr	Tyr	Cys	10	15	15																		
Thr	Ile	Arg	Val	Ala	Tyr	Gly	Thr	Ser	Ala	Gly	Ass	Ala	Gly	Phe	Trp	35	40	45																		
Ala	Leu	Gln	Leu	Leu	Ass	Lys	Val	Thr	Ser	Ala	Gly	Ass	Ala	Gly	Phe	Trp	Sor	Glo	Thr	Ser	Ala	Gly	Ass	Ala	Gly	Phe	Trp	Ala	Ala	Ile	Sor	Sor	Sor	Sor	Sor	Cor

<210> 372 <211> 71 <212> PRT <213> E. Coli

 $<\!\!400\!\!>$ 372 Met Ser Asn Lys Met Thr Gly Leu Val Lys Trp Phe Asn Ala Asp Lys 1 5 10 15 Gly Phe Gly Phe Ile Ser Pro Val Asp Gly Ser Lys Asp Val Phe Val

20 25 30

His Phe Ser Ala Ile Gln Asn Asp Asn Tyr Arg Thr Leu Phe Glu Gly 35 40 45

Gln Lys Val Thr Phe Ser Ile Glu Ser Gly Ala Lys Gly Pro Ala Ala 50 55 60

Ala Asn Val Ile Ile Thr Asp 65 70

<210> 373 <211> 338 <212> PRT <213> E. Coli

<400> 373 Met Phe Val Ile Trp Ser His Arg Thr Gly Phe Ile Met Ser His Gln 10 Leu Thr Phe Ala Asp Ser Glu Phe Ser Ser Lys Arg Arg Gln Thr Arg 20 25 30 Lys Glu Ile Phe Leu Scr Arg Met Glu Gln Ile Leu Pro Trp Gln Asn 35 40 45 Met Val Glu Val Ile Glu Pro Phe Tyr Pro Lys Ala Gly Asn Gly Arg 50 55 60 Arg Pro Tyr Pro Leu Glu Thr Met Leu Arg Ile His Cys Met Gln His 65 70 75 80 Trp Tyr Asn Leu Ser Asp Gly Ala Met Glu Asp Ala Leu Tyr Glu Ile 85 90 95 Ala Ser Met Arg Leu Phe Ala Arg Leu Ser Leu Asp Ser Ala Leu Pro 100 105 110 Asp Arg Thr Thr Ile Met Asn Phe Arg His Leu Leu Glu Gln His Gln 115 120 125 Leu Ala Arg Gln Leu Phe Lys Thr Ile Asn Arg Trp Leu Ala Glu Ala 130 135 140 Gly Val Met Met Thr Gln Gly Thr Leu Val Asp Ala Thr Ile Ile Glu 145 150 155 160 Ala Pro Ser Ser Thr Lys Asn Lys Glu Gln Gln Arg Asp Pro Glu Met 165 . 170 175 His Gln Thr Lys Lys Gly Asn Gln Trp His Phe Gly Met Lys Ala His 180 185 190 Ile Gly Val Asp Ala Lys Ser Gly Leu Thr His Ser Leu Val Thr Thr 195 200 205 Ala Ala Asn Glu His Asp Leu Asn Gln Leu Gly Asn Leu Leu His Gly 210 220 Glu Glu Gln Phe Val Ser Ala Asp Ala Gly Tyr Gln Gly Ala Pro Gln 225 230 235 240 Arg Glu Glu Leu Ala Glu Val Asp Val Asp Trp Leu Ile Ala Glu Arg 245 250 255 Pro Gly Lys Val Arg Thr Leu Lys Gln His Pro Arg Lys Asn Lys Thr 260 265 270 Ala Ile Asn Ile Glu Tyr Met Lys Ala Ser Ile Arg Ala Arg Val Glu 275 280 285 His Pro Phe Arg Ile Ile Lys Arg Gln Phe Gly Phe Val Lys Ala Arg 290 295 300 Tyr Lys Gly Leu Leu Lys Asn Asp Asn Gln Leu Ala Met Leu Phe Thr 305 310 315 320 Leu Ala Asn Leu Phe Arg Ala Asp Gln Met Ile Arg Gln Trp Glu Arg 325 330 Ser His

<210> 374 <211> 157 <212> PRT <213> E. Coli

<210> 375 <211> 372 <212> PRT <213> E. Coli

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195
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                                                       205
Val Phe Lys Asn Tyr Glu Leu Ile Ile Ser Ala Ala Arg Lys Leu Lys
210 215 220
Glu Gln Ser Asn Ile Lys Phe Leu Leu Thr Ile Ser Gly Thr Glu Asn 235 240
Ala Tyr Ala Lys Tyr Ile Ile Ser Leu Ala Glu Gly Leu Asp Asn Val
245 250 255
His Phe Leu Gly Tyr Leu Asp Lys Glu Lys Ile Asp His Cys Tyr Asn 260 265 270
Ile Ser Asp Ile Val Cys Phe Pro Ser Arg Leu Glu Thr Trp Gly Leu 275 280 285
Pro Leu Ser Glu Ala Lys Glu Arg Gly Lys Trp Val Leu Ala Ser Asp
290 295 300
Phe Pro Phe Thr Arg Glu Thr Leu Gly Ser Tyr Glu Lys Lys Ala Phe 305 310 315 320
Phe Asp Ser Asn Asn Asp Asp Met Leu Val Lys Leu Ile Ile Asp Phe 325 335
Lys Lys Gly Asn Leu Lys Lys Asp Ile Ser Asp Ala Asn Phe Ile Tyr 340 345 350
Arg Asn Glu Asn Val Leu Val Gly Phe Asp Glu Leu Val Asn Phe Ile
      355
                               360
Thr Glu Glu His
    370
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<210> 376 <211> 196 <212> PRT <213> E. Coli

<400> 376 Met Ile Leu Lys Leu Ala Lys Arg Tyr Gly Leu Cys Gly Phe Ile Arg 1 5 10 15 Leu Val Arg Asp Val Leu Leu Thr Arg Val Phe Tyr Arg Asn Cys Arg Ile Ile Arg Phe Pro Cys Tyr Ile Arg Asn Asp Gly Ser Ile Asn Phe 35 40 45 Gly Glu Asn Phe Thr Ser Gly Val Gly Leu Arg Leu Asp Ala Phe Gly 50 55 60 Arg Gly Val Ile Phe Phe Ser Asp Asn Val Gln Val Asn Asp Tyr Val 65 70 75 80 His Ile Ala Ser Ile Glu Ser Val Thr Ile Gly Arg Asp Thr Leu Ile 85 90 95 Ala Ser Lys Val Phe Ile Thr Asp His Asn His Gly Ser Phe Lys His
100 105 110 Ser Asp Pro Met Ser Ser Pro Asn Ile Pro Pro Asp Met Arg Thr Leu 115 120 125 Glu Ser Ser Ala Val Val Ile Gly Gln Arg Val Trp Leu Gly Glu Asn 130 135 140 Val Thr Val Leu Pro Gly Thr Ile Ile Gly Asn Gly Val Val Val Gly 145 150 155 160 Ala Asn Ser-Val Val Arg Gly Ser Ile Pro Glu Asn Thr Val Ile Ala 165 170 175 Gly Val Pro Ala Lys Ile Ile Lys Lys Tyr Asn His Glu Thr Lys Leu 180 185 Trp Glu Lys Ala

<210> 377 <211> 330 <212> PRT

<213> E. Coli

<400> 377 Met Tyr Phe Leu Asn Asp Leu Asn Phe Ser Arg Arg Asp Ala Gly Phe 10 15 Lys Ala Arg Lys Asp Ala Leu Asp Ile Ala Ser Asp Tyr Glu Asn Ile 20 25 30 Ser Val Val Asn Ile Pro Leu Trp Gly Gly Val Val Gln Arg Ile Ile 35 40 45 Ser Ser Val Lys Leu Ser Thr Phe Leu Cys Gly Leu Glu Asn Lys Asp 50 60 Val Leu Ile Phe Asn Phe Pro Met Ala Lys Pro Phe Trp His Ile Leu 65 70 75 80 Ser Phe Phe His Arg Leu Leu Lys Phe Arg Ile Val Pro Leu Ile His 85 90 95 Asp Ile Asp Glu Leu Arg Gly Gly Gly Gly Ser Asp Ser Val Arg Leu 100 105 110 Ala Thr Cys Asp Met Val Ile Ser His Asn Pro Gln Met Thr Lys Tyr 115 120 125 Leu Ser Lys Tyr Met Ser Gln Asp Lys Ile Lys Asp Ile Lys Ile Phe 130 135 140 Asp Tyr Leu Val Ser Ser Asp Val Glu His Arg Asp Val Thr Asp Lys 145 150 155 160 Gln Arg Gly Val Ile Tyr Ala Gly Asn Leu Ser Arg His Lys Cys Ser 165 170 175 Phe Ile Tyr Thr Glu Gly Cys Asp Phe Thr Leu Phe Gly Val Asn Tyr 180 185 190 Glu Asn Lys Asp Asn Pro Lys Tyr Leu Gly Ser Phe Asp Ala Gln Ser 195 200 205 Pro Glu Lys Ile Asn Leu Pro Gly Met Gln Phe Gly Leu Ile Trp Asp 210 215 220 Gly Asp Ser Val Glu Thr Cys Ser Gly Ala Phe Gly Asp Tyr Leu Lys 225 230 235 240 Phe Asn Asn Pro His Lys Thr Ser Leu Tyr Leu Ser Met Glu Leu Pro 245 250 255 Val Phe Ile Trp Asp Lys Ala Ala Leu Ala Asp Phe Ile Val Asp Asn 260 265 270 Arg Ile Gly Tyr Ala Val Gly Ser Ile Lys Glu Met Gln Glu Ile Val 275 280 285 Asp Ser Met Thr Ile Glu Thr Tyr Lys Gln Ile Ser Glu Asn Thr Lys 290 295 300 Ile Ile Ser Gln Lys Ile Arg Thr Gly Ser Tyr Phe Arg Asp Val Leu 305 310 315 320 Glu Glu Val Ile Asp Asp Leu Lys Thr Arg

<210> 378 <211> 388 <212> PRT <213> E. Coli

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Leu Thr Phe Thr Leu Ser Cys Leu Leu Thr Glu Ser Val Leu Asp Leu 65 70 75 80
                       70
                                              75
Asn Ile Arg Lys Val Asn Asn Ala Ile Tyr Ser Ile Pro Ser Lys Lys
85 90 95
Val His Asn Val Gly Leu Leu Val Ile Ser Phe Ser Met Ile Tyr Ile
100 105 110
Cys Met Arg Leu Ser Asn Tyr Gln Phe Gly Thr Ser Leu Leu Ser Tyr
115 120 125
Met Asn Leu Ile Arg Asp Ala Asp Val Glu Asp Thr Ser Arg Asn Phe
130 135 140
Ser Ala Tyr Met Gln Pro Ile Ile Leu Thr Thr Phe Ala Leu Phe Ile
145 150 155 160
Trp Ser Lys Lys Phe Thr Asn Thr Lys Val Ser Lys Thr Phe Thr Leu
165 170 175
Leu Val Phe Ile Val Phe Ile Phe Ala Ile Ile Leu Asn Thr Gly Lys
Gln Ile Val Phe Met Val Ile Ile Ser Tyr Ala Phe Ile Val Gly Val
195 200 205
Asn Arg Val Lys His Tyr Val Tyr Leu Ile Thr Ala Val Gly Val Leu
210 215 220
Phe Ser Leu Tyr Met Leu Phe Leu Arg Gly Leu Pro Gly Gly Met Ala 225 230 230 235
Tyr Tyr Leu Ser Met Tyr Leu Val Ser Pro Ile Ile Ala Phe Gln Glu
245 250 255
Phe Tyr Phe Gln Gln Val Ser Asn Ser Ala Ser Ser His Val Phe Trp 260 265 270
Phe Phe Glu Arg Leu Met Gly Leu Leu Thr Gly Gly Val Ser Met Ser 275 280 285
Leu His Lys Glu Phe Val Trp Val Gly Leu Pro Thr Asn Val Tyr Thr
290 295 300
Ala Phe Ser Asp Tyr Val Tyr Ile Ser Ala Glu Leu Ser Tyr Leu Met
305 310 315 320
Met Val Ile His Gly Cys Ile Ser Gly Val Leu Trp Arg Leu Ser Arg
325 330 335
Asn Tyr Ile Ser Val Lys Ile Phe Tyr Ser Tyr Phe Ile Tyr Thr Phe
340 345 350
Ser Phe Ile Phe Tyr His Glu Ser Phe Met Thr Asn Ile Ser Ser Trp 355 360 365
Ile Gln Ile Thr Leu Cys Ile Ile Val Phe Ser Gln Phe Leu Lys Ala
  370
                           375
                                                   380
Gln Lys Ile Lys
385
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<210> 379 <211> 367 <212> PRT <213> E. Coli

 <400>
 379

 Met
 Tyr
 Asp
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 Ile
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 Gly
 Ser
 Gly
 Leu
 Phe
 Gly
 Ala
 Val
 Cys
 Lys
 So
 Asp
 Lys
 Cys
 Gly
 Ile
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 Gly
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Ser Pro Leu Ala Ile Tyr Lys Asp Lys Leu Phe Asn Leu Pro Phe Asn 85 90 95 Met Asn Thr Phe His Gln Met Trp Gly Val Lys Asp Pro Gln Glu Ala 100 105 110 Gln Asn Ile Ile Asn Ala Gln Lys Lys Lys Tyr Gly Asp Lys Val Pro 115 120 125 Glu Asn Leu Glu Glu Gln Ala Ile Ser Leu Val Gly Glu Asp Leu Tyr 130 135 140 Gln Ala Leu Ile Lys Gly Tyr Thr Glu Lys Gln Trp Gly Arg Ser Ala 145 150 155 160 Lys Glu Leu Pro Ala Phe Ile Ile Lys Arg Ile Pro Val Arg Phe Thr 165 170 175 Phe Asp Asn Asn Tyr Phe Ser Asp Arg Tyr Gln Gly Ile Pro Val Gly 180 185 190 Gly Tyr Thr Lys Leu Ile Glu Lys Met Leu Glu Gly Val Asp Val Lys 195 200 205 Leu Gly Ile Asp Phe Leu Lys Asp Lys Asp Ser Leu Ala Ser Lys Ala 210 215 220 His Arg Ile Ile Tyr Thr Gly Pro Ile Asp Gln Tyr Phe Asp Tyr Arg 225 230 235 240 Phe Gly Ala Leu Glu Tyr Arg Ser Leu Lys Phe Glu Thr Glu Arg His 245 . 250 255 Glu Phe Pro Asn Phe Gln Gly Asn Ala Val Ile Asn Phe Thr Asp Ala 260 265 270 Asn Val Pro Tyr, Thr Arg Ile Ile Glu His Lys His Phe Asp Tyr Val 275 280 285 Glu Thr Lys His Thr Val Val Thr Lys Glu Tyr Pro Leu Glu Trp Lys 290 295 300 Val Gly Asp Glu Pro Tyr Tyr Pro Val Asn Asp Asn Lys Asn Met Glu 305 310 315 320 Leu Phe Lys Lys Tyr Arg Glu Leu Ala Ser Arg Glu Asp Lys Val Ile 325 330 335 Phe Gly Gly Arg Leu Ala Glu Tyr Lys Tyr Tyr Asp Met His Gln Val 340 345 Ile Ser Ala Ala Leu Tyr Gln Val Lys Asn Ile Met Ser Thr Asp 355 360

<210> 380 <211> 371 <212> PRT <213> E. Coli

130 135 140 Ala Gly Leu Val Leu Met Val Val Ser Cys Leu Val Thr Leu Glu Leu Thr Gly Ile Thr Val Ser Phe Asn Ser Ala Pro Leu Glu Trp Trp Leu
170 175 145 Ser Leu Pro Ile Ile Val Ile Tyr Pro Leu Leu Phe Gly Trp Val Ser 180 185 190 Tyr Gln Thr Ala Thr Lys Leu Ala Glu His Lys Arg Arg Leu Gln Val Met Ser Thr Arg Asp Gly Met Thr Gly Val Tyr Asn Arg Arg His Trp 210 215 220 Glu Thr Met Leu Arg Asn Glu Phe Asp Asn Cys Arg Arg His Asn Arg 225 230 235 240 Asp Ala Thr Leu Leu Ile Ile Asp Ile Asp His Phe Lys Ser Ile Asn 245 250 255 Asp Thr Trp Gly His Asp Val Gly Asp Glu Ala Ile Val Ala Leu Thr 260 265 270 Arg Gln Leu Gln Ile Thr Leu Arg Gly Ser Asp Val Ile Gly Arg Phe 275 280 285 Gly Gly Asp Glu Phe Ala Val Ile Met Ser Gly Thr Pro Ala Glu Ser 290 295 300 Ala Ile Thr Ala Met Leu Arg Val His Glu Gly Leu Asn Thr Leu Arg 305 310 315 320 Leu Pro Asn Thr Pro Gln Val Thr Leu Arg Ile Ser Val Gly Val Ala 325 330 335 Pro Leu Asn Pro Gln Met Ser His Tyr Arg Glu Trp Leu Lys Ser Ala 340 345 350 Asp Leu Ala Leu Tyr Lys Ala Lys Lys Ala Gly Arg Asn Arg Thr Glu 355 360 365 Val Ala Ala 370

<210> 381 <211> 467 <212> PRT <213> E. Coli

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Ala Trp Val Ser Tyr Phe Gly Gly Asn Phe Asn Gly Asp Asn Gly Thr
210 215 220
Ile Asn Tyr Asp Gln Asp Val Asn Gly Ile Met Val Gly Val Asp Thr 225 230 235 240
Lys Ile Asp Gly Asn Asn Ala Lys Trp Ile Val Gly Ala Ala Ala Gly
245 250 255
Phe Ala Lys Gly Asp Met Asn Asp Arg Ser Gly Gln Val Asp Gln Asp 260 265 270
Ser Gln Thr Ala Tyr Ile Tyr Ser Ser Ala His Phe Ala Asn Asn Val
275 280 285
Phe Val Asp Gly Ser Leu Ser Tyr Ser His Phe Asn Asn Asp Leu Ser 290 295 300
Ala Thr Met Ser Asn Gly Thr Tyr Val Asp Gly Ser Thr Asn Ser Asp 305 310 315 320
Ala Trp Gly Phe Gly Leu Lys Ala Gly Tyr Asp Phe Lys Leu Gly Asp
325 330 335
Ala Gly Tyr Val Thr Pro Tyr Gly Ser Val Ser Gly Leu Phe Gln Ser
340 345 350
Gly Asp Asp Tyr Gln Leu Ser Asn Asp Met Lys Val Asp Gly Gln Ser
355 360 365
Tyr Asp Ser Met Arg Tyr Glu Leu Gly Val Asp Ala Gly Tyr Thr Phe 370 385 380

Thr Tyr Ser Glu Asp Gln Ala Leu Thr Pro Tyr Phe Lys Leu Ala Tyr 385 390 395 400
Val Tyr Asp Asp Ser Asn Asn Asp Asn Asp Val Asn Gly Asp Ser Ile
405
415
Asp Asn Gly Thr Glu Gly Ser Ala' Val Arg Val Gly Leu Gly Thr Gln
420
425
430
Phe Ser Phe Thr Lys Asn Phe Ser Ala Tyr Thr Asp Ala Asn Tyr Leu
435 440 445
Gly Gly Gly Asp Val Asp Gln Asp Trp Ser Ala Asn Val Gly Val Lys
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                               455
                                                         460
Tyr Thr Trp
465
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<210> 382 <211> 222 <212> PRT <213> E. Coli

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 Met
 Pro Val
 Lys
 Asp
 Leu
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 Gly
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 Thr
 Ala
 Lys
 Asp
 Ala
 Gln
 Met

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Asp Ala Phe Tyr Trp Leu Ala Trp Gln Asn Arg Ile Leu Glu Leu Arg 130 135 140 Asp Val Gln Leu Ile Gly His Asn Ser Tyr Glu Gln Ile Arg Ala Thr 145 150 155 160 Leu Leu Ser Met Ile Asp Trp Asn Glu Glu Leu Arg Ser Arg Ile Gly
165 170 175 Val Met Asn Tyr Ile His Gln Arg Thr Arg Ile Ser Arg Ser Val Val Ala Glu Val Leu Ala Ala Leu Arg Lys Gly Gly Tyr Ile Glu Met Asn 195 200 205 Lys Gly Lys Leu Val Ala Ile Asn Arg Leu Pro Ser Glu Tyr 215

<210> 383 <211> 84 <212> PRT <213> E. Coli

<400> 383 Met Thr Asp Lys Ile Arg Thr Leu Gln Gly Arg Val Val Ser Asp Lys $1 \hspace{1cm} 5 \hspace{1cm} 10 \hspace{1cm} 15$ Met Glu Lys Ser Ile Val Val Ala Ile Glu Arg Phe Val Lys His Pro 20 25 30 Ile Tyr Gly Lys Phe Ile Lys Arg Thr Thr Lys Leu His Val His Asp 35 40 Glu Asn Asn Glu Cys Gly Ile Gly Asp Val Val Glu Ile Arg Glu Cys 50 55 60 55 60 Arg Pro Leu Ser Lys Thr Lys Ser Trp Thr Leu Val Arg Val Val Glu 65 70 80 Lys Ala Val Leu

<210> 384 <211> 63 <212> PRT <213> E. Coli

<400> 384 Met Lys Ala Lys Glu Leu Arg Glu Lys Ser Val Glu Glu Leu Asn Thr Glu Leu Leu Asn Leu Leu Arg Glu Gln Phe Asn Leu Arg Met Gln Ala 20 25 30 Ala Ser Gly Gln Leu Gln Gln Ser His Leu Leu Lys Gln Val Arg Arg 35 40 45 Asp Val Ala Arg Val Lys Thr Leu Leu Asn Glu Lys Ala Gly Ala 55

<210> 385 <211>-136 <212> PRT <213> E. Coli

Met Leu Gln Pro Lys Arg Thr Lys Phe Arg Lys Met His Lys Gly Arg 10 Asn Arg Gly Leu Ala Gln Gly Thr Asp Val Ser Phe Gly Ser Phe Gly 20 25 30 Leu Lys Ala Val Gly Arg Gly Arg Leu Thr Ala Arg Gln Ile Glu Ala

<210> 386 <211> 233 <212> PRT <213> E. Coli

<400> 386 Met Gly Gln Lys Val His Pro Asn Gly Ile Arg Leu Gly Ile Val Lys
1 5 10 15 Pro Trp Asn Ser Thr Trp Phe Ala Asn Thr Lys Glu Phe Ala Asp Asn 20 25 30 Leu Asp Ser Asp Phe Lys Val Arg Gln Tyr Leu Thr Lys Glu Leu Ala 35 40 45 Lys Ala Ser Val Ser Arg Ile Val Ile Glu Arg Pro Ala Lys Ser Ile
50 55 60 Arg Val Thr Ile His Thr Ala Arg Pro Gly Ile Val Ile Gly Lys Lys 65 70 75 80 Gly Glu Asp Val Glu Lys Leu Arg Lys Val Val Ala Asp Ile Ala Gly 85 90 95 Val Pro Ala Gln Ile Asn Ile Ala Glu Val Arg Lys Pro Glu Leu Asp 100 105 110 Ala Lys Leu Val Ala Asp Ser Ile Thr Ser Gln Leu Glu Arg Arg Val Met Phe Arg Arg Ala Met Lys Arg Ala Val Gln Asn Ala Met Arg Leu 130 135 140 Gly Ala Lys Gly Ile Lys Val Glu Val Ser Gly Arg Leu Gly Gly Ala
145 150 155 160 Glu Ile Ala Arg Thr Glu Trp Tyr Arg Glu Gly Arg Val Pro Leu His 165 170 175 Thr Leu Arg Ala Asp Ile Asp Tyr Asn Thr Ser Glu Ala His Thr Thr 180 185 190 Tyr Gly Val Ile Gly Val Lys Val Trp Ile Phe Lys Gly Glu Ile Leu 195 200 205 Gly Gly Met Ala Ala Val Glu Gln Pro Glu Lys Pro Ala Ala Gln Pro 210 215 220 215 220 Lys Lys Gln Gln Arg Lys Gly Arg Lys 230

<210> 387 <211> 110 <212> PRT <213> E. Coli

<400> 387

 Met
 Glu
 Thr
 Ile
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 Ala
 Gln
 Lys

 Val
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 Leu
 Ala
 Asp
 Leu
 Ile
 Arg
 Gly
 Lys
 Lys
 Val
 Ser
 Gln
 Ala

 Leu
 Asp
 Ile
 Leu
 Thr
 Tyr
 Thr
 Asp
 Lys
 Lys
 Ala
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 Ile
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 Ala
 Lys
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 Ile
 Arg

<210> 388 <211> 92 <212> PRT <213> E. Coli

<210> 389 <211> 273 <212> PRT <213> E. Coli

130 | 135 | 140 | 140 | 141 | 155 | 140 | 141 | 155 | 160 | 160 | 155 | 160 | 160 | 155 | 160 | 175 | 160 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 | 175 |

<210> 390 <211> 100 <212> PRT <213> E. Coli

<210> 391 <211> 201 <212> PRT <213> E. Coli

Gly Gly Val Thr Phe Ala Ala Arg Pro Gln Asp His Ser Gln Lys Val 85 90 95 95

Asn Lys Lys Met Tyr Arg Gly Ala Leu Lys Ser Ile Leu Ser Glu Leu 105 110 105 110

Val Arg Gln Asp Arg Leu Ile Val Val Glu Lys Phe Ser Val Glu Ala 120 125

Pro Lys Thr Lys Leu Leu Ala Gln Lys Leu Lys Asp Met Ala Leu Glu 130 135 140

Asp Val Leu Ile Ile Thr Gly Glu Leu Asp Glu Asn Leu Phe Leu Ala 155 160

Ala Arg Asn Leu His Lys Val Asp Val Arg Asp Ala Thr Gly Ile Asp 165 170 175

Pro Val Ser Leu Ile Ala Phe Asp Lys Val Val Met Thr Ala Asp Ala 180 185 190

Val Lys Gln Val Glu Glu Met Leu Ala 185 190

<210> 392 <211> 209 <212> PRT <213> E. Coli

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<210> 397 <211> 642 <212> PRT <213> E. Coli

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245 250 255 Gln Glu Glu Ala Pro Gly Met Val Phe Trp His Asn Asp Gly Trp Thr 260 265 270 Ile Phe Arg Glu Leu Glu Val Phe Val Arg Ser Lys Leu Lys Glu Tyr 275 280 285 Gln Tyr Gln Glu Val Lys Gly Pro Phe Met Met Asp Arg Val Leu Trp 290 295 300 Glu Lys Thr Gly His Trp Asp Asn Tyr Lys Asp Ala Met Phe Thr Thr 305 310 315 320 Ser Ser Glu Asn Arg Glu Tyr Cys Ile Lys Pro Met Asn Cys Pro Gly 325 330 335 His Val Gln Ile Phe Asn Gln Gly Leu Lys Ser Tyr Arg Asp Leu Pro Leu Arg Met Ala Glu Phe Gly Ser Cys His Arg Asn Glu Pro Ser Gly 355 360 365 Ser Leu His Gly Leu Met Arg Val Arg Gly Phe Thr Gln Asp Asp Ala 370 375 380 His Ile Phe Cys Thr Glu Glu Gln Ile Arg Asp Glu Val Asn Gly Cys 385 390 395 400 Ile Arg Leu Val Tyr Asp Met Tyr Ser Thr Phe Gly Phe Glu Lys Ile
405 410 415 Val Val Lys Leu Ser Thr Arg Pro Glu Lys Arg Ile Gly Ser Asp Glu
420 425 430 Met Trp Asp Arg Ala Glu Ala Asp Leu Ala Val Ala Leu Glu Glu Asn 435 440 445 Asn Ile Pro Phe Glu Tyr Gln Leu Gly Glu Gly Ala Phe Tyr Gly Pro Lys Ile Glu Phe Thr Leu Tyr Asp Cys Leu Asp Arg Ala Trp Gln Cys 465 470 475 480 Gly Thr Val Gln Leu Asp Phe Ser Leu Pro Ser Arg Leu Ser Ala Ser 485 490 495 Tyr Val Gly Glu Asp Asn Glu Arg Lys Val Pro Val Met Ile His Arg
500 505 510 Ala Ile Leu Gly Ser Met Glu Arg Phe Ile Gly Ile Leu Thr Glu Glu 515 520 525

Phe Ala Gly Phe Phe Pro Thr Trp Leu Ala Pro Val Gln Val Val Ile 530 535 540 Met Asn Ile Thr Asp Ser Glm Ser Glu Tyr Val Asn Glu Leu Thr Gln 545 550 560 Lys Leu Ser Asn Ala Gly Ile Arg Val Lys Ala Asp Leu Arg Asn Glu 565 570 575 Lys Ile Gly Phe Lys Ile Arg Glu His Thr Leu Arg Arg Val Pro Tyr 580 585 590 Met Leu Val Cys Gly Asp Lys Glu Val Glu Ser Gly Lys Val Ala Val
595
600
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Arg Thr Arg Arg Gly Lys Asp Leu Gly Ser Met Asp Val Asn Glu Val
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100 105 110

Gly Phe Ala Arg Phe Val Asp Ala Lys Thr Leu Glu Val Asn Gly Glu
115 120 125 Thr Ile Thr Ala Asp His Ile Leu Ile Ala Thr Gly Gly Arg Pro Ser 130 135 140

His Pro Asp Ile Pro Gly Val Glu Tyr Gly Ile Asp Ser Asp Gly Phe 145 150 155 160 Phe Ala Leu Pro Ala Leu Pro Glu Arg Val Ala Val Val Gly Ala Gly 165 170 175 Tyr Ile Ala Val Glu Leu Ala Gly Val Ile Asn Gly Leu Gly Ala Lys 180 185 190 Thr His Leu Phe Val Arg Lys His Ala Pro Leu Arg Ser Phe Asp Pro 195 200 205 Met Ile 55r Glu Thr Leu Val Glu Val Met Asn Ala Glu Gly Pro Gln 210 225 220

Leu His Thr Asn Ala Ile Pro Lys Ala Val Val Lys Asn Thr Asp Gly 230 235 240 Ser Leu Thr Leu Glu Leu Glu Asp Gly Arg Ser Glu Thr Val Asp Cys
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425

420

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Met Arg 450
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2894

60

76

1549

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<210> 402 <211> 1549 <212> RNA <213> E. Coli

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       <223> Primer Oligonucleotide
       <400> 403
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       <400> 404
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atcaccagca gatgasataa cgataaccag aacaacgcct tatagcgttg agtttgcgag
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aaaacgttca tattgtacct ttttgattaa ccattgggg
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                                                                        120
ataaggggac aaagngaagg aagtggntat taangganno gocaatgoga nttagggcag
                                                                        180
accattegge cattegeett ettggttate gaagtteate cagatageeg ttgeengaee
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gaccagatto gottonggoa caaagcocca gtaacggotg toogcgotgt tgtogoggtt
                                                                        300
gtcgcccatc atgaagtatt gtcccggagg aacaatccag gttgccagtt gttgccctgg
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ctgctggtaa tacatcccca cctgatcctg cgcaatcggc actgtcagaa tgcggtgcgt
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cacatcacce agtgtetett tacgetegga aagacgaatt ceatttett tggtttegtt
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tttcggcact tcaaagaatc cgctggtcgc ttccccacca ttacggcgtg agaaggtctg
                                                                        540
aacgaaatcg ctcggttcca cgtttgagta ggtgaccggc agcgcgtttt cacacgcctg
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gacgtaagcg gatggagtgg ccggaaacct catagtgacc gcccaccagt tggcctgcat
                                                                           180
cgctttgtag cgtacgcgcg gcattggcaa taagattcag atactcagac tcttccgggg
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cettegecag cataaaagag gaggatgete gegtatgeag caactgetee agegeaaatt
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gcagccgcgg ttgagtatca ctgaataaag gatcgttttc gtcaatcaaa tgtggctgag
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tggtcaaagt tgatgtttt tagtctgttg tcaaagccgc nattataccn gtaaccggca
                                                                           420
                                                                           480
ctacagcaca cgtagaaagc acccgacaat actcctggca tgggcgttaa agctcacagg
                                                                           540
atggagatet tttetteact ggeetaaaaa getgatatte tgtaaagagt tacaengtaa
                                                                           600
cattgagatc gctatgaaat atcaacaact tggaaaatct tgnaaagcng gttggaaaat
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ggaaagtatc tggttaagaa gc
                                                                           682
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<211> 309
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tttggcctta cttaacggag aaccattaag ccttaggacg cttcacgcca tacttggaac
                                                                           180
gagcctgctt acggtcttta acgccggagc agtcaagcgc accacgtacg gtgtggtaac
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gaacacccgg gaggtettta acacgaccge cacggatcag gatcacggag tgeteetgea
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qccaagctt
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                                                                           120
cagaacggac gtcctgtcgc agtatattaa gtcgtcgata gaaacaagca ttgaaaggca
cagcagtagt caaacagtgt gaaacgctac tggcgcctta cagcgcaaaa aggctggtga
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ttgctcacgc cttctttcag agcagccggt gcagattcta ccaggtcttt agcttctttc
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catttaaatk gttcctgaat atcagaataa gtttatacgt aagcgaatgc gttaaaaaga
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taactgcgaw taagcagctt ytttcgcatc gcgtacagma gccagagtac gaaccagttt
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gccagccgaa gcttctttca tggttgccat caggcgtgca attgcttctt cgtaggtcgg
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                                                                          900
tttgacctca aattttgcat tcgctttcgc gaactctttg aacagacgag cagcagegee
                                                                          960
cgggtgttcc atagagtatg caatcagggt cggaccaaca aacgcgtctt tcaggcactc
                                                                         1020
gaacggagta ccttcaacag cacggcgcag cagggtgtta cgaacaacac gcatgtatac
                                                                         1080
gccagetteg egacetgett taegeagtte agteattta tetacagtta egeceaeggg
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                                                                         120
 togatagaaa caagcattga aaggcacago agtagtcaaa cagtgtgaaa cgctactggo
                                                                         180
 gccttacagc gcaaaaaggc tggtgactaa aaagtcacca gccatcagcc tgatttctca
                                                                         240
 ggctgcaacc ggaagggttg gcttatttaa cttcaacttc agcgccagct tcttccagag
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                                                                        120
ttacacagaa cggacgtcct gtcgcagtat attaagtcgt cgatagaaac aagcattgaa
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                                                                        300
cttatttaac ttcaacttca gcgccagctt cttccagagc ttttttcagt gcttctgcgt
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cgtetttget cacgcettet ttcagagcag ccgggtgcag attctaccag gtetttaget
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tettteagae ceaggeeagt tgegeeacgt actgetttga taacageaac tttgttageg
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ccagcagett teagaattac gtegaattea agttttttet teagcagett caacegggee
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tcaagttcta caacgtccat tacagacata gctgcaactg cttcaatgat tkgatcttwa
                                                                        660
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                                                                        720
taaaaagata actgcgatta agcagettet ttegcatege gtacageage cagaggtega
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agcaataaaa aataataaca atgatataaa totaatgttt ttaaatatat tgtottttat
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                                                                            360
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tactgcttan cgctaccagt ttgtctgccc tggcggttgt aacgccagat cggtacccgt
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 oggaetttta coogcotggt ttattaattg cactgtnato ogggegttog coogcottaa
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 tcacaatagg ctgtgtagec tgggcctgtt tetettteac ccgcgccaga gcggcagcaa
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 togoatottt atotttggot geaggttgaa oggotgogot ottatgtogt toaaggogag
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 ccgettttte gegetecaga cgageetgge gegettegaa acgegetttg gettetgegg
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 getggttcag taaggtacca ggagaaactt caggaagctt gtactcgaca atacagtttg
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tgtttttttg gagatctacg gtaaaattaa gcgaatccga tgagactgtg cagccataat
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cgaggacgcg cccgctaatt ttaataacgc tatctgcgga taaagcagaa taggtggtta
                                                                         240
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cgacagattg ctgtctgctg gttcagtaag gtaccaggag a
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<211> 697
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<213> Escherichia coli
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cgggcgctga ttcttcccac gcggttattt tggcacacac cagatccagc aaggggtttt
                                                                         180
caggategtt gageageaga tgatetacea gttecagege etgggtgtat tgtteetegt
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totgaataco ogocagaaaa ggtgccacag cagttagctt ttotcotgct tgcaagatgt
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cggcaatcgc aatcatttt teeeettagt acgatgaaca geggtaaaga aategtatte
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tttatgcgtc ataacttcac gtatgtagca cttttgcgat tcaaaaaaga ccattgctac
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aacacgtaat tcattgcccc caacattgaa aacataatgc ttatccagat atttgaagtt
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atccagagat gggaatactg cttttaatga ctcaggtttt ttgaaatatc ccttagcaat
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cgtgktcccc agagccacca actccgtttt atgttgcggg tatttttccg cagcatcttt
                                                                         600
caatgetttt tgagttatea ggtgeattet teateaegte egtkgmeaaa ttggeaatat
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<212> DNA
<213> Escherichia coli
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                                                                         120
accatasagg tcgagggcgc ttaagatgtt aaaaacccgc tatccgttaa aaaacaatgt
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tcaactaagg tcagtgacat tgcgctaaaa aagcg
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WO 00/44906 PCT/US00/02200 <210> 448 <211> 395 <212> DNA <213> Escherichia coli <400> 448 gcattattca tgagaaatgt gtatcgtaaa tcaactgaaa ttaacgcaac catttgttat ttaaggttta attatctgtg tgtgatattt tattgaatgt tttaaatatt gtttttattg gcattgctat aatattggtt atcatttgct gaatggattc agtcttaatg agtgggtttt 180 taagggacag gcatagagta atgatacgta tgcataacca acatctttac tcattatgtc attgaatgtt gacgctatgt gtttatgagg gagaggtatt ttcagttgat ctggattgtt 240 300 aaattcatat aatgcgcctt tgctcatgaa tggatgccag tatgtagtgg gaaattataa 360 atattgaaat agtccaacta cttctttatt accaa 395 <210> 449 <211> 641 <212> DNA <213> Escherichia coli <220> <221> misc_feature <222> (1) ... (641) <223> n = A, T, C or Gataatcaggt aagaaaaggt gcgcggagat taccgtgtgt tgcgatatat tttttagttt 60 cgcgtggcaa tacatcagtg gcaataaaac gacatatcca gaaaaatata cactaagtga 120 atgatatett eegatttate ttaategttt atggataaeg geaaaggget tegttttte 180 ctatacttat tcagcactca caaataaagg aacgccaatg aaaattatac tctgggctgt 240 attgattatt ttcctgattg ggctactggt ggtgactggc gtatttaaga tgatatttta 300 aaattaatta atgtcatcag gtccgaaaat aacgagaata tttcagtctc tcatcctgtt 360 gegeteetgt catgtgeatt getteatata ateaetggeg caaggagege egeaggegna 420 gnntgenegn egneceacet nacceeatge egaactteag aantgaaaac neentaacne 480 cgatngtcgg cgggngcctc cccatgenan agtangggaa ntgccangcg nennattaaa 540 cgaaaggctn attncaaaga ctgggccttn cntttatctg atgtttgtcg gagaacgctc 600 tectgagnan gacaaatnee geegggageg gatttgaaen t <210> 450 <211> 314 <212> DNA <213> Escherichia coli <221> misc_feature <222> (1)...(314) <223> n = A, T, C or Ggaactacgag taagaatagc tncgaattcc cgtttatgga taacggcaaa gggcttcgtt 60 ttttcctata cttattcagc actcacaaat aaaggaacgc caatgaaaat tatactctgg 120 gctgtattga ttattttcct gattgggcta ctggtggtga ctggcgtatt taagatgata 180 ttttaaaatt sattaatgtc atcaggtccg aaaataacga gaatatttca gtctctcatc 240 ctgttgcgct cctgtcatgt gcattgcttc atataatcac tggcgcaagg agcgcgcagg 300 gggntntnnt cttt 314 <210> 451 <211> 236

<212> DNA

<400> 451

<213> Escherichia coli

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tatactctgg gctgtattga ttattttcct gattgggcta ctggtggtga ctggcgtatt
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atcgtttatg gataacggca aagggcttcg tttttccta tacttattca gcactcacaa
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ataaaggaac gccaatgaaa attatactct gggctgtatt gattattttc ctgattgggc
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tactggtggt gactggcgta tttaagatga tattttaaaa ttaattaatg tcatcaggtc
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cgaaaataac gagaatattt cagtototca tootgttgcg ctcctgtcat gtgcattgct
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cgctgcctaa acggctggaa gaagcgggtt ttgcgtttcg ctggtacgat ttagaagagg
                                                                       180
cgctggcgga tgtcgttcgc tgatgtggtt tacagcaaac atccgccagt taactcccgg
                                                                       240
tgttacagga ttagtggctt tgcgcgataa gatcgtctgg tgaaagtcgg gtcaccatca
                                                                       300
taactaactc totgtotaaa cototatooa goatotootg agcaatacgc agggottott
                                                                       360
cgtgtttgcc ctgcattgcg ccttcttcac gtaatctgtc agcaatggtc atcaagtttc
                                                                       420
tectttett gtggtgegeg tteegetate teaccaataa atgeaegaaa acgetgggea
                                                                       480
tcccctgttt gtaatacgta attaaacagg gcttttagct gtctgtcatt agtgktccct
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gtaactagca g
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<212> DNA
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<400> 454
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ggttttgctg ttatccattg agtcacggaa ctg
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<211> 232
<212> DNA
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                                                                      120
acaaaatggg tgcagtacat actcgttgga aatcaacaca ggaggctggg aatgccgcag
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<210> 456
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<213> Escherichia coli
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cacqaacgcg gtcgacttta tcgtagtcga tttctgggaa gatgatctgc tcacggacac
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ccatgctgta gttaccacga ccgtcgaaag acttagcgga caggccacgg aagtcacgga
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tacgaggtac agcaatagtg atcaggcgct caaagaactc ccacatgcgt tcgccacgca
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gagttacttt acagcogatc ggatagccct gacggatttt gaagcctgca acagatttgc
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ccagcagttt tttgtcagcg atcgcttcac caacacccat gttcagggtg atcttctcga
                                                                        480
cccgagggac ttgcatgaca gaattgtagt taaactcagt catgagtttt ttaactactt cgtctttgta gtaatcatgc agtttcgcca tcgtactact ccatgtcggt gaacgctctc
                                                                       540
                                                                       600
ctgagtagga caaatccgcc ggagccggat ttaacgttgc gaacaaccgn cccggagggg
                                                                       660
tggnggcagg accocgccat aactggcagc attaaattaa gcagaaggcc atc
                                                                       713
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<213> Escherichia coli
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gtttttagtt ttgcttaaaa atattgttag ttttattaaa tgcaaaacta aattattggt
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240
tagggttata aatgcgacta ccatgaagtt tttaattgaa agtattgggt tg
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<211> 282
<212> DNA
<213> Escherichia coli
ttattaaatg caaaactaaa ttattggtat catgaatttg ttgtatgatg aataaaatat
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                                                                       120
taattgaaag tattgggttg ctgataattt gagctgttct attctttta aatatctata
                                                                       180
taggtctgtt aatggatttt atttttacaa ttttttgtgt ttaggcatat aaaaatcaac
                                                                       240
ccgccatatg aacggcgggt taaaatattt acaacttagc aa
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<210> 459
<211> 300
<212> DNA
<213> Escherichia coli
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                                                                       120
ggggggcagc aaggggctga aacgggaaag cccctcccga agaaggggcc ttgtataagg
                                                                       180
aaagggttat gatgaagctc gtcatcatac tggttgtgtt gttactgtta agtttcccga
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cttactaaca actcatcaga ggggggagaa atcctccctt acccttgttc ctttactcta
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                                                                         120
gtgttgttac tgttaagttt cccgacttac taacaactca tcagagggg gagaaatcct
                                                                         180
cccttaccct tgttccttta ctctaggttg aaaaaacaac agcgtcaata ggcctgccat
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gtacgaagcg agatotgtga accgotttoc ggttagcott ttttatoctg ttg
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<210> 461
<211> 359
<212> DNA
<213> Escherichia coli
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ttcacgcttt tatttttcac ctggatgata agagattcac tgtgtgaatt gcatattaaa
                                                                         120
caggagagtt atgagctggc ggcgttttta gcctgcaaat tgaaagagta agagtcttcg
                                                                         180
gcgggaaatt attcccgcct tacttacggc gttgcgcatt ctcattgcac ccaaatttat
                                                                         240
tottoacaaa aataataata gattttatta ogogatogat tatttattto otgaaaacaa
                                                                         300
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ggetttgaca tattaggggc tattccattt catcgtccaa caaaatgggt gcagtacata
                                                                         180
ctcgttggaa atcaacacag gaggctggga atgccgcaga aatatagatt actttcttta
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atagtgattt gtttcacgct tttattttc acctggatga taagagattc actgtgtgaa
                                                                         300
ttgcatatta aacaggagag ttatgagctg gcggcgtttt tagcctgcaa attgaaagag
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taagagtett eggegggaaa ttatteeege ettaettaeg gegttgegea tteteattge acceaaattt attetteaca aaaataataa tagatttat taegegateg attatttatt
                                                                         420
                                                                         480
teetgaaaac aaataaaaaa ateecegeea aatggeaggg atettagatt etgtgetttt
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aagcagagaa tacaggctgg ttacgttacc agctgccggg cctttagcgc cgctttcgat
                                                                         600
ggtgaaggac actttctgac cttcgtccag agatttgtaa ccatcgttct ggatagcaga
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acaacacagg cggctatatg acgttcgcag agctgggcat ggccttctgg catgatttag
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cggctccggt cattgctggc attcttgcca gtatgatcgt gaactggctg aacaagcgga
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caggggggaa actotgcggc ctttttcgtt cttactgcgg gtaaggcacc cagtcgccgc
                                                                         360
cgttcaggcg aacgtacggt ttatcctggt attgaataac tactgcattt gagttctcgg
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agaccggtgc tgtttgtggc aacccactgg tgagtttttt ccagtcaaca ttgtcttcgg
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                                                                         540
gttgttcgat gacaatcggt gccccctgat gcggtgcctt catgccgaag aatttcaccc
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caacggggac gtcggtgata gacgggctag
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<212> DNA
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 aaaaaatttg agggataagg coggaatggo tooggocaga gggaagttaa cogcgaagct
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tggcccagcg gaccagcata ttaggatggc gaatcgtcca gatcgccatc acgctactgc
                                                                               240
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 caaccagege ceaggagege agacttagea geatatteea gegacgateg taagegeetg
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                                                                               391
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 <213> Escherichia coli
 <400> 465
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                                                                               120
 gactaatgaa cggagataat ccctcaccta accggcccct tgttacagtt gtgtacaagg
                                                                              180
 ggcctgattt ttatgacggc gaaaaaaaac cgccagtaaa ccggcggtga atgcttgcat
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 ggatagattt gtgttttgct tttacgctaa caggcatttt cctgcactga taacgaatcg
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ttgacacagt agcatcagtt ttctcaatga atgttaaacg gagcttaaac tcggttaatc
                                                                              360
acattttgtt cgtcaataaa catgcagcga tttcttccgg tttgcttacc ctcatacatt
gcccggtccg ctcttccaat gaccacatcc agaggctctt caggaaatgc gcgactcaca
                                                                              420
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aactggcaaa ttctgacacc tgcacgacat gcttcttcat cattagccgc tttgacaata
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atgataaatt cttcgcccc gtagc
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<212> DNA
<213> Escherichia coli
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tettteggta teagecagag agtgagacea aaaatgataa tegtatacat aagtettteg
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ccaccgaagc ccggaggtgg tgaaataaaa ccgggcacaa cacgaaggcg catttccgat
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                                                                              420
                                                                              480
gatgtccgcc ctttttaaag tgaattttgt gatgcggtga atgcggctaa gcgcacgtgg
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cacagttaaa agtcatgtta gtccttattg gtttgggtgg gaaagccgac tgtaattgtt
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<212> DNA
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agcatcttgt aaagccttta tcgttttttt atgctctgga ttaatataat cactacatct
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<210> 469 <211> 261 <212> DNA <213> Esci	nerichia col	i				
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<210> 470 <211> 98 <212> DNA <213> Esch	erichia col	i				
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<210> 471 <211> 259 <212> DNA <213> Esch	erichia col	i				
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<210> 472 <211> 94 <212> DNA <213> Esch	erichia col:	i				
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<210> 473 <211> 174 <212> DNA <213> Esch	erichia coli	i.				
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acagcatogo catooggoa	c tgatacgagg	tttatttcag	ctcatcaacc	atcg	174
<210> 474 <211> 138					
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